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British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017

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NICE accredited
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NICE has accredited the process used by the British Association of Dermatologists to produce guidelines. The renewed accreditation is valid until 31 May 2021 and applies to guidance produced using the process described in Updated guidance for writing a British Association of Dermatologists clinical guidance – the adoption of the GRADE methodology 2016. The original accreditation term began on 12 May 2010. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

1.0 PURPOSE AND SCOPE

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of pemphigus vulgaris (PV). The document aims to update and expand on the previous guidelines by:

- offering an appraisal of all relevant literature from January 2000 up to May 2016, focusing on any key developments
- address important, practical clinical questions relating to the primary guideline objective.
- providing guideline recommendations and, where appropriate, with some health economic implications
- discussing potential developments and future directions

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic (see section 29), in addition to an updated Patient Information Leaflet (PIL; available on the BAD website, http://www.bad.org.uk/for-the-public/patient-information-leaflets).

1.1 Exclusions

This guideline does not cover other forms of pemphigus.

2.0 STAKEHOLDER INVOLVEMENT AND PEER REVIEW

The guideline development group (GDG) consisted of consultant dermatologists and a clinical nurse specialist in medical dermatology. One of the dermatologists is also an oral medicine specialist. The draft document was circulated to the British Association of Dermatologists (BAD) membership, British Dermatological Nursing Group (BDNG), Primary Care Dermatological Society (PCDS), Pemphigus Vulgaris Network and PEM Friends (UK) for comments, which were actively considered by the GDG, and peer-reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Sub-committee) prior to publication.

3.0 METHODOLOGY

This set of guidelines has been developed using the BAD recommended methodology[1] and with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument [www.agreetrust.org].[2] Recommendations were developed for implementation in the NHS using a process of considered judgment based on the evidence. PubMed, MEDLINE, EMBASE and LILACS databases were searched for PV from January 2000 up to May 2016; search terms and strategies are detailed as a web appendix. Additional relevant references were also isolated from citations in reviewed literature. All identified titles were screened and those relevant for first-round inclusion were selected for further scrutiny. The abstracts for the shortlisted references were then reviewed by the GDG and the full papers of relevant material obtained; disagreements in the final selections were resolved by discussion with the entire GDG. The structure of the 2003 guidelines was then discussed and re-evaluated, with headings and sub-headings decided; different co-authors were allocated separate sub-sections. Each co-author then performed a detailed appraisal of the

selected literature with discussions within the GDG to resolve any issues. All sub-sections were subsequently collated, circulated within the GDG and edited to produce the final guidelines.

4.0 LIMITATIONS OF THE GUIDELINE

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English language references was a pragmatic decision but the authors recognize this may exclude some important information published in other languages.

5.0 PLANS FOR GUIDELINE REVISION

The proposed revision date for this set of recommendations is scheduled for 2022; where necessary, important interim changes will be updated on the BAD website.

6.0 BACKGROUND

PV is an acquired autoimmune disease in which IgG antibodies target desmosomal proteins to produce intraepithelial, mucocutaneous blistering. Desmoglein 3 is the major antigen but 50% to 60% of patients have additional antibodies to desmoglein 1, the antigen targeted in pemphigus foliaceus (PF).[3-5] Although the pathogenesis of PV is complex, involving multiple pathways,[6] the underlying antibody profile is a major determinant of the clinical phenotype of PV.[5,7,8]

The average mortality of PV was 75% before the introduction of corticosteroids in the early 1950s.[9] This figure may be an underestimate due to lack of diagnostic criteria, inclusion of all subtypes of pemphigus and of other blistering disorders such as bullous pemphigoid, which have a better prognosis. However, not all cases of PV have such a dismal prognosis. Studies differentiating the clinical phenotypes have shown a lower mortality in patients with predominantly mucosal PV (1% to 17%) compared with those with mucocutaneous PV (8% to 42%).[10-12] Mucocutaneous PV tends to be a more severe disease, proving slower to respond to treatment and less likely to achieve remission off-treatment than purely mucosal PV.[13]

6.1 Clinical presentation

The diagnosis of PV should be suspected in any patient with mucocutaneous erosions or blisters. The oral mucosa is the first site of involvement in the majority of cases and PV may remain confined to the mucosal surfaces or extend to involve the skin (average lag period of 4 months).[14-16] Diagnostic delay is very common when PV is confined to the oral mucosa.[17] A

minority will present with cutaneous erosions but oral erosions will, eventually, occur in most cases. PV presents across a wide age range with peak frequency in the third to sixth decades.

7.0 LABORATORY DIAGNOSIS

Perilesional skin biopsies should be taken for histology and direct immunofluorescence (DIF). In patients with isolated oral disease, a histology specimen should be taken from perilesional mucosa and a DIF sample taken from an uninvolved area ideally from the buccal mucosa.[18] Suprabasal acantholysis and blister formation is highly suggestive of PV but the diagnosis should be confirmed by the characteristic deposition of IgG and/or complement ~~in the intercellular spaces of the epidermis~~on the cell surfaces of epithelial keratinocytes. Indirect immunofluorescence (IIF) is less sensitive than DIF[19-21] but may be helpful if a biopsy is difficult, e.g. children and uncooperative adults. Commercial enzyme-linked immunosorbent assays (ELISA) are available for direct measurement of desmoglein 1 and desmoglein 3 antibodies in serum. They potentially offer advantages over IIF, such as increased sensitivity, but are not helpful in cases in which there are other antigens.[22-24] Therefore, IIF and ELISA should be considered complementary and DIF remains the gold standard diagnostic investigation.[25] Five millilitres of blood is sufficient for both IIF and ELISA. Saliva is potentially a useful alternative to serum for ELISA; there is emerging evidence that desmoglein 3 IgG is detectable in saliva by ELISA with a similar sensitivity to serum (61% saliva vs. 74% serum).[26]

In patients with oral pemphigus, an intra-oral biopsy is the optimum but IIF or DIF on a skin biopsy may suffice. One study showed that the sensitivity of DIF was 71% in oral biopsies compared with 61% in normal skin taken from 28 patients with oral PV.[27] Another study reported that the sensitivity of DIF was 89% in oral biopsies compared with 85% for IIF.[15] If there are no skin lesions and a sample for DIF is to be taken from the oral mucosa, the buccal mucosa can be exposed by everting the cheek, placing the thumb at the commissure and reflecting the corner of the mouth, applying external pressure on the cheek with the index finger to present the buccal mucosa.

The transport medium into which samples for DIF are placed varies, including saline, Michel's medium and snap freezing into liquid nitrogen.[28] Liquid nitrogen gives good preservation of immunoreactants but has practical disadvantages. However, it has been shown in one study using matched biopsy specimens that transportation in saline, for up to ~~24~~ 48 hours, gave superior results~~,~~ to liquid nitrogen, providing a more practical and cost-effective medium for getting samples to the lab.[29] Transportation in saline for up to 24 hours was optimum[29] and Michel's medium is favoured for longer transportation times.[28]

8.0 FURTHER INVESTIGATIONS

The following additional investigations should be considered prior to commencing treatment: full blood count and differential, urea and electrolytes, liver function tests, fasting glucose and HbA1C, fasting lipids, antinuclear antibody (differential of pemphigus erythematosus), urinalysis, blood pressure, weight, height (children) and a pregnancy test in females at risk of pregnancy. Current guidelines on prevention of osteoporosis[30] should be followed, so a bone

density scan early in the course of treatment may be needed. In anticipation of using an adjuvant immunosuppressant, appropriate recommended additional investigations and vaccinations should be undertaken. A baseline measure of disease activity (see section 9.1) and quality of life, supplemented by IIF and ELISA titres if facilities exist, will be useful for disease monitoring and judging treatment responses (see sections 9.0-9.2).

9.0 DISEASE MONITORING

Decisions concerning ongoing disease management will be based on making an assessment of disease activity. The simplest way of monitoring disease activity is clinically, which can be done more objectively by using clinical disease scoring systems. Clinical disease activity assessment can be supplemented with immunological measures and quality of life scores.

9.1 Disease severity scoring

Numerous disease severity scoring systems exist making it difficult to compare data between studies. Two validated severity scoring systems which have become frontrunners are the pemphigus disease area index (PDAI) and the autoimmune bullous skin disorder intensity index (ABSIS),[31-34] each taking 2-5 minutes to complete.[32,34] These have also been validated for use in oral PV but are inferior to another system, the oral disease severity score (ODSS), which may be combined with ABSIS or PVDAI in patients with skin or extra-oral mucosal sites.[35]

It is recommended that disease severity is scored in routine clinical practice. It is essential in clinical trials.

9.2 Immunological monitoring

IIF can be used to express the quantity of pemphigus antibodies in serum as a series of discontinuous serum dilutions. It is subjective and operator-dependent and the titre depends on the substrate used, due to variable amounts of antigen being expressed at different sites. In general, mucosal substrates are better for detection of desmoglein 3 antibodies and skin better for detection of desmoglein 1 antibodies, with the use of both substrates enhancing sensitivity.[36] IIF titres can reflect disease activity but the relationship is not perfect and examples of active disease with negative IIF or vice versa exist such that IIF cannot be relied upon for disease monitoring. Whether IIF using two substrates is more useful for disease monitoring is yet to be demonstrated.

Desmoglein 1 and 3 ELISAs are sensitive and specific assays providing an objective and quantitative measure of antibody levels. In general, ELISA levels are related to disease activity, with desmoglein 1 antibody levels associated with skin severity and desmoglein 3 levels associated with oral severity.[37-41] Titres usually fall with treatment and disease remission.[40,42-45] Patients followed over time also show fluctuations in ELISA levels that mirror disease activity[37,41] but as with IIF, the relationship is not perfect: examples of patients with inactive disease and high ELISA titres and vice versa are reported,[37,42-44] and one study found that changes in desmoglein 3 antibody levels did not correlate with clinical activity.[43]

Some of these problems reflect saturation of the ELISAs at higher values which could be overcome by increasing the serum dilution.[46]

The use of sequential salivary anti-desmoglein 3 IgG titres as a biomarker of disease activity is an emerging area of interest and titres have recently been shown to reflect oral disease activity.[26]

In general, falling or persistently low and negative IIF or ELISA titres are a good sign; such that immunosuppression could be tapered. Rising or persistently high titres should be a cause for concern. Where facilities exist to follow titres, the information could be used as an adjunct to clinical assessment but due to the imperfections of the assays discussed, good clinical judgement remains paramount.

10.0 EVALUATING THERAPIES IN PEMPHIGUS VULGARIS

In general, the quality of published data concerning the therapy of PV is poor. There are few good quality randomized controlled trials (RCTs). The majority of data is confined to case reports and small case series in which PV cases of variable severity may be included, often with other subtypes of pemphigus. Follow-up periods are often short, even in the larger trials, and dosing schedules vary widely. Trial design is often poor, with different drug combinations used in different arms such that any differences in outcomes cannot be attributed to a single intervention. Controls are often indirect, involving comparisons of remission and mortality rates with historical controls or comparison of maintenance corticosteroid doses before and after the addition of a given therapy. A huge number of outcome measures and disease definitions have also been used, making comparison between studies difficult. Finally, the rarity of PV means recruitment of sufficient numbers of patients is challenging; many studies are small and underpowered.

To address some of these issues, the International Pemphigus Committee has produced a consensus statement which outlines definitions of important time points and disease status.[47] In parallel, efforts are being made to use commonly accepted disease severity scores.[32,33] By using a commonly accepted set of core outcome measures, it is envisaged that trial data can be better compared and pooled such that small and underpowered individual studies could become of value as it would be possible to include them in larger meta-analyses. In addition, it is now widely acknowledged that the rarity of PV means cooperative research with multiple recruitment sites are needed to produce successful trials with adequate power.[48] It has been estimated that to demonstrate a 20% difference between interventions with 80% power, a study of more than 196 patients would be needed in PV.[49] Trials such as these, using a set of core outcome measures, are coming into being but at present, in most studies, it is difficult to judge the effect of individual drugs and make firm treatment recommendations. In these guidelines, we have listed the highest ranking level of evidence and given an overall recommendation for each therapy. A summary of treatment options is given in section 29.

11.0 GENERAL PRINCIPLES OF MANAGEMENT

PV is an uncommon and potentially life-threatening disease requiring immunosuppressive treatment. It should be managed by secondary care physicians experienced in the treatment of autoimmune mucocutaneous diseases. The management of active oral PV with systemic therapies should be approached in the same way as the management of active skin disease and could be managed by dermatologists where oral medicine expertise is not available.

The management of PV can be considered in two main phases: **induction of remission** and **maintenance of remission**.

Remission induction: the initial aim of treatment is to induce **disease control**, defined as new lesions ceasing to form and established lesions beginning to heal.[47] Corticosteroids are the most effective and rapidly acting treatment for PV, hence are critical in this phase. Using corticosteroids, disease control typically takes several weeks to achieve (median 3 weeks).[50] During this phase the intensity of treatment may need to be built up rapidly to suppress disease activity. Although adjuvant drugs are initiated during this phase in general, their immediate therapeutic benefit is relatively limited because of their slower onset. They are rarely used alone to induce remission in PV.

After disease control is achieved there follows a **consolidation** phase during which drug doses used to induce disease control are continued. The end of this consolidation phase is defined arbitrarily as being reached when 80% of lesions have healed, both mucosa and skin, and there have been no new lesions for at least 2 weeks.[47] This phase may be relatively short, but could be considerably longer if there is extensive cutaneous ulceration. Healing of oral ulceration tends to take longer than that for skin, with the oral cavity often the last site to clear in those with mucocutaneous PV. The end of the consolidation phase is the point at which most clinicians would begin to taper treatment, usually the corticosteroid dose. Premature tapering of corticosteroids, before disease control is established and consolidated, is not recommended.

Remission maintenance: after induction there follows a maintenance phase during which treatment is gradually reduced (see section 12), in order to minimize side-effects, to the minimum required for disease control. The ultimate goal of treatment should be to maintain remission on 10 mg prednisolone daily or less, with 10 mg being the dose designated arbitrarily as 'minimal therapy' by international consensus.[47] ~~Occasional blisters are acceptable and indicate that the patient is not being over treated.~~ PV is a chronic disease, and in one study, 36% of patients required at least 10 years of treatment.[51]

Systemic corticosteroids are the most important element of remission induction and consolidation. In general, adjuvant drugs are slower in onset than corticosteroids. Their main role is in remission maintenance. Adjuvant drugs are combined commonly with corticosteroids with the aim of increasing efficacy and reducing maintenance corticosteroid doses and subsequent corticosteroid side effects. Although mortality and complete remission rates have improved since the introduction of adjuvant drugs, this is in comparison with historical controls. Until 2017, ~~T~~there had been~~are~~ no prospective, high-quality controlled studies that demonstrated conclusively the presumed benefits of adjuvant drugs in PV.[52] Therefore, some authorities ~~do not~~have not used adjuvant drugs unless there ~~are~~ were contraindications or side effects of corticosteroids, or if tapering the corticosteroids dose

was associated with repeated relapses.[9] ~~However, s~~Some trials ~~have~~ demonstrated lower cumulative corticosteroid doses, but without a difference in primary disease outcome measures, for azathioprine, cyclophosphamide and mycophenolate mofetil;[53-55] which we believe ~~this~~ is a clinically relevant outcome. A systematic review and meta-analysis, which included 10 trials and pooled adjuncts together, concluded that they were not beneficial for achieving remission but collectively decreased risk of relapse by 29%.[55] Despite ~~this~~ sparsity of evidence, it was commonly believed that adjuvant drugs were likely to be beneficial, as proven in other areas of autoimmunity, and most centres use them as standard practice. In 2017, the first RCT conclusively demonstrating the benefit of an adjuvant drug was published: rituximab combined with short-term prednisolone showed superior efficacy compared to prednisolone alone, with rates of complete remission of PV, off all treatment, of 89% compared with 28% at 2 years.

An overview of PV management, with the aim of providing a brief reference for the clinical setting, is summarised in Table 1 and a more detailed description follows.

First-line therapy	Corticosteroids: • Oral prednisolone – optimal dose not established but suggest start with prednisolone 1 mg/kg/day (or equivalent) in most cases, 0.5-1 mg/kg in milder cases. • Increase in 50-100% increments every 5-7 days if blistering continues (see below* for guidance on maximum dose) • Consider pulsed intravenous corticosteroids if >1 mg/kg oral prednisolone required, or as initial treatment in severe disease followed by 1 mg/kg/day oral prednisolone. • Taper dose once remission induced and maintained, with absence of new blisters and healing of the majority of lesions (skin and mucosal). Aim to reduce to 10 mg daily or less. • Assess risk of osteoporosis immediately • Effective in all stages of disease, including remission induction Combine corticosteroids with an adjuvant immunosuppressant • Azathioprine 2 to 3 mg/kg/day (if TPMT normal) • Mycophenolate mofetil 2 to 3 g/day • Rituximab** (RA protocol, 1 g x2 infusions, 2 weeks apart) More important for remission maintenance than induction, due to delayed onset Good skin and oral care is essential.
Second-line therapy	Consider switching to alternate corticosteroid sparing agent if treatment failure with first-line adjuvant drug* (azathioprine, ~~or~~ mycophenolate mofetil or rituximab) or mycophenolic acid 720 to 1080 mg twice daily if GI symptoms from mycophenolate mofetil.
Third-line therapy	Consider choice of additional treatment options based on assessment of individual patient need and consensus of MDT. Options include: ~~• Rituximab (RA protocol, 1 g x2 infusions, 2 weeks apart)~~ • Cyclophosphamide

	• Immunoadsorption • Intravenous immunoglobulin (IVIG) • ~~Cyclophosphamide~~ • Methotrexate • Plasmapheresis or plasma exchange • ~~Immunoadsorption~~
***Treatment failure** Defined by international consensus[47] as continued disease activity or failure to heal despite 3 weeks of prednisolone 1.5 mg/kg/day, or equivalent, or any of the following, given for 12 weeks: • azathioprine 2.5 mg/kg/day (assuming normal TPMT) • mycophenolate mofetil 1.5 g twice daily • cyclophosphamide 2 mg/kg/day • methotrexate 20 mg/week **Rituximab is currently approved by NHS England as a third-line treatment for pemphigus. Regulatory authorities in many other countries have not yet approved rituximab as a first-line treatment.	
Abbreviations: TPMT, thiopurine methyl transferase; GI, gastrointestinal; MDT, multidisciplinary team; RA, rheumatoid arthritis.	

Table 1: An overview of the management of pemphigus vulgaris

Treatment withdrawal is a realistic aim, with one study reporting rates of complete remission off-therapy of 38%, 50% and 75% achieved in 3, 5 and 10 years from diagnosis, respectively.[56] Another study reported 59% of patients were off treatment after a mean treatment duration of 3 years and this outcome was not associated with initial disease severity.[57] However, withdrawal of treatment should be cautious and not done prematurely; relapse rates are high initially, with 47% of successfully treated patients relapsing in one trial when treatment was stopped after 1 year.[58]

12.0 ORAL CORTICOSTEROIDS *(Strength of recommendation B, Level of evidence1+; see Appendix 1)*

Systemic corticosteroids are the best established therapy for the management of PV. Their introduction in the early 1950s resulted in a dramatic fall in mortality to an average of 30%,[9] with complete remission rates off-therapy of 13% to 20%.[9,59] Outcomes have continued to improve and recent studies have shown that the rate of complete remission on low-dose corticosteroids (prednisolone 10 mg/day or less) is 52% to 76% at 1 year with very few deaths.[53,54,60,61]

Clinical improvement may be seen within days of starting corticosteroids and on average, cessation of blistering takes 2 to 3 weeks[50,53,61-64] whilst full healing may take 3 to 8 weeks.[50,61,65] IIF titres fall with corticosteroid treatment but lag behind clinical improvement.[66]

The optimum corticosteroid dosing schedule is not known and dosing schedules are largely empirical and based on practical experience. Early studies advocated high doses, e.g. initial doses of 120 to 400 mg/day prednisolone.[62,65] However, corticosteroid side effects were

common and dose-related[67,68] with one study estimating that up to 77% of deaths were corticosteroid-related.[67] Therefore, a more moderate approach to corticosteroid therapy has been advocated. However, only one RCT has compared dosing schedules; initial therapy with low-dose prednisolone (30 to 60 mg/day) was compared with high-dose prednisolone (120 to 180 mg/day) in patients with severe pemphigus (19 with PV, three with PF) affecting more than 50% of their body surface. There was no significant difference in the duration to achieve initial disease control nor in relapse rates at 5 years, and there were no deaths.[63] However, it should be noted that the dose tapered more rapidly in the high-dose arm so that on average, by week 7 and thereafter, the daily corticosteroid dose was lower in the 'high-dose' arm. In contrast, a retrospective study showed benefit with higher corticosteroid doses: treatment with prednisolone 1.5 mg/kg led to significantly shorter times to achieve initial disease control and remission compared with prednisolone 40 mg on alternate days combined with azathioprine, although there were fewer side effects in the low-dose arm.[60]

It is common practice worldwide to initiate treatment at 1 to 2 mg/kg prednisolone or equivalent[51,53,54,61,69-73] with a majority of clinicians experienced in managing PV choosing 1 mg/kg.[69] However, milder cases may be treated with more conservative corticosteroid doses e.g. 0.5 to 1 mg/kg; tailored dosing according to disease severity is well established [9,65] and appropriate,[74] with no evidence to indicate that long-term outcomes are influenced by the intensity of initial treatment.[57,74]

If there is no response within 5 to 7 days, it is suggested that the dose should be increased in 50% to 100% increments until disease control is achieved, i.e. no new lesions and the onset of healing in pre-existing ones.[9,61,65,71,75] If prednisolone doses above 1 mg/kg/day are required, pulsed intravenous corticosteroids should be considered. Treatment failure for oral corticosteroids has been defined by international consensus as failure to achieve disease control despite 3 weeks of prednisolone 1.5mg/kg/day or equivalent.[47]

Once remission is induced and maintained with healing of the majority of lesions, both skin and oral, the dose of corticosteroids can be tapered cautiously. This includes assessing oral lesions which are often the last site to heal. The mouth and other mucosal sites must be examined in addition to the skin. Tapering before disease control is established and consolidated is not recommended. There is no established tapering schedule and those published in clinical trials vary widely,[53,54,58,61,63,71,72,75-79] with the dose by week 12 varying from 5 mg[75] to 60 mg daily.[79] The average tapering rate across these trials was 6 mg per week in the first 3 months.

A 50% reduction every 2 weeks has been suggested.[9] The GDG consensus is to initially reduce the daily dose by 5 to 10 mg of prednisolone every 2 weeks down to 20 mg daily, then 2.5 mg every 2-4 weeks down to 10 mg daily and thereafter slowly reduce in increments of 1 mg. Prednisolone doses of 10 mg or less should be the aim of treatment, defined by international consensus as minimal therapy in PV.[47]

Relapses in the short-term can be managed by increasing the corticosteroid dose although there is no consensus on the optimum way to manage relapses. They are often milder than initial disease presentation and are managed typically with lower corticosteroid doses. Various approaches to managing relapses have been suggested including reverting to the previous corticosteroid dose at which there was disease control;[80] doubling the corticosteroid

dose,[61,63,72] with 50% incremental increases thereafter until disease control;[61] increasing to prednisolone 40 mg/day, or if already greater than this, to the previous dose at which disease control was achieved;[71] increasing prednisolone dose by 10 to 20 mg/day.[50,81] Relapses that are more severe should be treated with corticosteroid doses as described for the initial presentation. At the time of relapse, in addition to increasing corticosteroid dose, long-term management should also be considered as relapses may recur when the corticosteroid doses are tapered again. It may be appropriate to add an adjuvant drug, increase the dose of an existing adjuvant or switch to an alternative, if the current adjuvant drug has been given at sufficient dose for at least 3 months (see table 1).

It is strongly recommended that guidelines for the prevention of corticosteroid-induced osteoporosis are followed.[30,82] A prednisolone dose of 7.5mg or more for 3 months or longer is considered a risk factor in those aged under 40 and any dose for those aged over 40.[82] Thus, all PV patients are at risk, assuming they are likely to exceed these limits, and bone health should be considered immediately upon commencing treatment because the rate of bone loss is most marked in the first 6 months of treatment.[83]

Summary
Systemic corticosteroids are a well-established and very effective treatment for PV. They should be used as first-line therapy.

13.0 PULSED INTRAVENOUS CORTICOSTEROIDS *(Strength of recommendation D (GPP), Level of evidence 4)*

This refers to the intermittent administration of high doses of corticosteroids, usually intravenous methylprednisolone (10 to 20 mg/kg or 250 to 1000 mg) or equivalent doses of dexamethasone given on up to 5 consecutive days.[84] Generally, pulsed corticosteroids are given intravenously but can be delivered orally.[85] The theoretical aims of 'pulsing' are to achieve more rapid and effective disease control compared with conventional oral dosing, thus allowing a reduction in long-term maintenance of corticosteroid doses and corticosteroid side effects. These theoretical benefits have not been demonstrated conclusively. In a well-designed, double-blind RCT, monthly oral dexamethasone pulses were of no additional benefit and were associated with more adverse effects compared with conventional oral corticosteroids and azathioprine.[76] However, this study was limited by small numbers (20 patients, eleven and nine in each arm) and a relatively short follow-up (1 year). One small, retrospective case-controlled study concluded that pulsed intravenous methylprednisolone (one course of 250 to 1000 mg/day for 2 to 5 days in eight cases; two courses in one case) resulted in increased complete remission rates (44% vs. 0%) and lower mean maintenance oral corticosteroid doses in nine patients with recalcitrant PV compared with six controls.[86] In terms of the rapidity of disease control, a retrospective case series reported signs of improvement within a week of pulsed methylprednisolone in all 12 patients[87] but similar responses have been reported with oral corticosteroids.

Summary
There is no evidence that pulsed corticosteroids are superior to conventional oral corticosteroids for maintenance of most cases of PV. However, short-term pulsed corticosteroids could be considered in severe or recalcitrant PV to induce remission,

particularly if there has been no response to high oral doses. There is no good evidence to support their use in this situation but the personal experience of the GDG is that pulsing is very useful for rapid disease control in patients with severe disease.

14.0 ADJUVANT DRUGS

14.1 Azathioprine *(Strength of recommendation B, Level of evidence 1+)*

a. Introduction

Azathioprine is a commonly prescribed adjuvant drug in PV and was first used successfully in 1969 by Krakowski *et al*.[88] Numerous small case series have reported a corticosteroid-sparing effect.[89-92] The complete remission rates of 28% to 45% exceed those seen in historical controls treated with corticosteroids alone.[9,59,91] Mortality rates of 1.4% to 7% are lower than those seen in historical controls treated with corticosteroids alone.[9,10,59,91]

b. Azathioprine as a single agent

In three cases, azathioprine was used successfully as a monotherapy to induce and maintain clinical remission with a fall in antibody titre.[90,93] However, there is a latent period of at least 6 weeks before the effects of azathioprine are seen[89-91,93] and its use as a monotherapy to induce remission should therefore be reserved for mild cases only, if a delay in achieving disease control can be tolerated.

c. Comparison with oral corticosteroids

The role of azathioprine as a corticosteroid-sparing drug has been demonstrated in a number of small studies. Chaidemenos *et al.* compared high-dose prednisolone (1.5 mg/kg/day) (n=17) with low-dose prednisolone (40 mg on alternate days) plus azathioprine 100 mg/day (n=19) in a retrospective comparison.[60] Both regimens were effective. Analysis of the 30 responders showed that the high-dose prednisolone group achieved a faster remission with greater side effects. The combination group had a significantly lower total prednisolone usage but a longer time until complete or partial remission. This was not an intention-to-treat analysis and the study was not powered adequately. In a retrospective study, described in section 14.3b, the time to remission and complete remission off-treatment showed no significant difference when adding azathioprine (100 mg/day) to prednisolone (100 mg/day starting dose).[94] In a large, unblinded RCT described in section 18.1, patients randomized to the prednisolone plus azathioprine arm (n=30) had required lower cumulative corticosteroid doses at 1 year than those treated with prednisolone alone (n=30), although efficacy was similar in these two arms.[53] In a subsequent study, the same authors performed a double-blind RCT comparing prednisolone (initial dose 2 mg/kg/day; n=28) plus placebo with prednisolone plus azathioprine (2.5 mg/kg/day; n=28) over 12 months.[95] Disease severity was measured using the Pemphigus Vulgaris Disease activity Index (PVDAI) and included an intention-to–treat analysis. No significant difference was seen in the mean PVDAI scores nor corticosteroid doses between the two groups over the 12 months. However, subgroup analyses revealed differences in the two arms towards the end of the trial: in the final 3 months there were significant differences in the PVDAI, mean daily and cumulative prednisolone dose, favouring prednisolone plus azathioprine. The mean PVDAI of the prednisolone-only group was 2.41 and the prednisolone plus azathioprine was 0.47 (p=0.045 ITT).

d. Comparison with other adjuvant drugs

Trials comparing azathioprine with mycophenolate mofetil and cyclophosphamide are described in section 18. In summary, two trials have compared azathioprine with mycophenolate mofetil[53,71] and there is evidence to suggest azathioprine has a superior corticosteroid-sparing effect.[52] There is also some evidence that azathioprine may be less effective at achieving disease control.[52,71] One retrospective study suggested azathioprine might be less effective than oral cyclophosphamide.[94] Three trials have compared azathioprine with pulsed cyclophosphamide regimens: one RCT showed no significant differences;[70] a non-randomized trial favoured pulsed cyclophosphamide which showed a lower cumulative corticosteroid dose although efficacy was similar;[72] a single-centre RCT showed lower cumulative corticosteroid doses in the azathioprine arm compared with the pulsed cyclophosphamide arm which did not reach significance in the authors' analysis[53] but was considered significant in an independent Cochrane review.[52]

Summary

Azathioprine is a well-established choice as an adjuvant drug for the management of pemphigus. A reasonable duration of treatment is needed to test efficacy and treatment failure should only be determined after at least 3 months at a dose of 2.5 mg/kg in patients with normal TPMT levels.[47] Although there remains a lack of high-quality prospective randomized trials there is some evidence to suggest that the co-administration of azathioprine reduces the cumulative corticosteroid dose and has a superior corticosteroid-sparing effect compared to mycophenolate mofetil.

14.2 Mycophenolate mofetil *(Strength of recommendation B, Level of evidence 1+)*

a. Introduction

Mycophenolate mofetil is often used as a first-line adjuvant to corticosteroid agents. Total daily doses of 2 to 3 g are given typically in two divided doses with prednisolone, i.e. 1 to 1.5 g twice daily. In patients who experience gastrointestinal side effects, mycophenolic acid can be given as an alternative, with the approximate equivalent doses being 720 to 1080 mg twice daily.

Several small, unblinded trials have suggested that mycophenolate mofetil is beneficial in pemphigus treatment. In a series of 12 patients who had relapsed on corticosteroids plus azathioprine, 11 improved on mycophenolate mofetil (2 g/day) and prednisolone (2 mg/kg), allowing a reduction in the prednisolone dose to 5 mg/day or less during the follow-up of 1 year. The patients responded rapidly, with a fall in IIF titres, and were free of lesions within 8 weeks of initiating mycophenolate mofetil.[96] However, based on nine patients, Nousari*et al*. commented that higher doses of mycophenolate mofetil (2.5 to 3 g/day) were often required to induce remission in PV and at least 8 weeks of treatment was necessary before clinical and immunological improvement was observed.[97] There have been more than 30 case series since these. Examples of the number of patients achieving disease control in previously refractory PV patients then treated with mycophenolate mofetil as a corticosteroid sparing agent include 71% (22/31),[98] 73% (8/11),[99] and 78% (14/18).[100] Few adverse effects were reported.

b. Comparison with oral corticosteroids

In the study described in section 18.1, 30 PV patients were given prednisolone alone (initial dose 2 mg/kg) and in another 30 it was combined with mycophenolate mofetil (1g twice daily) in this single-centre unblinded RCT.[53] There were no significant differences in efficacy in these two arms. The cumulative corticosteroid dose in the mycophenolate mofetil arm was lower but did not reach statistical significance.[52]

In an unblinded RCT,[61] 47 patients (36 PV, 11 PF) were allocated randomly to receive methylprednisolone alone vs methylprednisolone (initially 1 mg/kg prednisolone equivalent) and mycophenolate mofetil (1.5 g twice daily). Disease activity was scored according to the number of lesions present. The authors reported no difference in the time to achieve disease control, induction of partial and complete remissions on or off minimal therapy, or the total amount of corticosteroids administered. There was no difference in the frequency of relapses or the development of side-effects and complications.[61]

There has been one double–blinded, placebo-controlled RCT.[54] In this multicentre study, 94/96 randomized patients were treated and 75 completed the study. Patients were allocated to either prednisone 1-2 mg/day (initial dose) plus placebo (n=37), prednisone plus mycophenolate mofetil 2 g/day (n=22) or prednisone plus mycophenolate mofetil 3 g/day (n=37). The primary outcome measure was the proportion of patients in each arm responding to treatment as determined by an absence of new or persistent lesions and a prednisone dose of ≤ 10 mg daily dose from weeks 48 to 52. While the authors found no significant difference in the primary endpoints, the time to initial response was faster and the time to a sustained response was 12 weeks shorter in both mycophenolate mofetil-treated arms. In addition, the cumulative corticosteroid dose taken over weeks 12 to 52 of the study was significantly lower in the combined mycophenolate mofetil arm compared to the placebo arm (P=0.028). Efficacy was similar in both mycophenolate mofetil arms but infectious adverse events were higher in those taking 3 g daily. In both these arms infections were commoner than in the placebo arm.[54]

c. Comparison with other adjuvant drugs

Studies comparing mycophenolate mofetil with azathioprine and cyclophosphamide are described in section 18. In summary, there is evidence that mycophenolate mofetil has an inferior corticosteroid-sparing effect compared with azathioprine[52,53,71] but may be more effective at achieving disease control.[52,71] Adverse events were not significantly different in these two studies but one did show fewer grade 3 and 4 adverse events with mycophenolate mofetil.[71] Mycophenolate mofetil has an inferior corticosteroid-sparing effect compared with pulsed cyclophosphamide.[52]

Summary

On the basis of current evidence, there is evidence that mycophenolate mofetil has a corticosteroid-sparing effect. It could be considered as an alternative to azathioprine in patients unresponsive to treatment or where co-morbidities/baseline investigations preclude azathioprine. It has a more favourable side-effect profile than azathioprine and is well tolerated. Treatment failure has been defined by international consensus as failure to respond to 3 g daily for 3 months.[47]

14.~~11~~03 Rituximab *(Strength of Recommendation B, Level of Evidence ~~2++~~1+)*

a. Introduction

Rituximab is a chimeric murine-human monoclonal antibody of immunoglobulin G1 (IgG1) sub-class, directed against the B lymphocyte-specific antigen CD20,[101] expressed by early B cells in the bone marrow, autoantigen-specific B cells, memory B cells and mature B cells. Following treatment with rituximab there is rapid and sustained depletion of circulating and tissue-based B cells that is maintained for at least 6 to 12 months. Recent data suggest that rituximab may also affect T cell function and modulate autoreactive T cells and production of T cell cytokines.[102]

b. Efficacy

An unblinded RCT of 90 newly diagnosed and treatment-naïve patients with moderate and severe PV (n=74) and PF (N=16) were treated with rituximab (1g days 0 and 14 and 0.5g at 12 and 18 months) in combination with short-term prednisolone (0.5-1 mg/kg for 3-6 months) compared with prednisolone alone (1-1.5 mg/kg for 12-18 months).[45] There was a significant difference in primary outcome: 89% of patients in the rituximab arm were in complete remission off all treatment at 2 years compared with 34% of patients treated with prednisolone alone (p<0.0001). The rates were 89% vs 28% in those with PV (p<0.0001). There were fewer severe adverse events in the rituximab treated patients, which probably reflects the fact that prednisolone doses were higher and more prolonged in those treated with prednisolone alone. The lack of blinding is a flaw of this trial, and in particular the risk of withdrawal bias as drop-out rates were higher in the prednisolone only arm. However, re-analysis assuming all withdrawals in the prednisolone-only arm went on to achieve remission off treatment still leads to a highly significant result. Nevertheless, the guideline group felt it appropriate to downgrade the recommendation rating to a B based on this single unblinded RCT.

~~Whilst there are currently no double-blind RCTs of the use of rituximab in the treatment of pemphigus, m~~ ~~Other~~Previous studies of rituximab have considered its ~~largely~~ used ~~it~~ in patients resistant to other therapies: multiple case series (reviewed in Ahmed *et al.* and Wang *et al.*)[103,104] suggest that it ~~it~~ is of utility in the treatment of PV, PF and paraneoplastic pemphigus with rates of remission in refractory disease of up to 86% following a single cycle of treatment.[105] In a meta-analysis of 578 patients with pemphigus (496 PV), remission was achieved in 76% of patients following a single cycle of rituximab, and 39% were able to come off adjuvant treatments.[104] In this study the mean time to disease control and remission was 1.1 and 5.8 months, respectively. Relapse occurred in 40% after an average duration of 14.5 months. Similar data is reported in an analysis of 451 PV patients from case series: remission was achieved in 74% to 87% after a single cycle (16% to 58% remained on other therapies, 27% to 58% off adjuvant treatments).[103] They reported clinical responses within 6 weeks and a relapse rate of up to 65% occurring 13 to 17 months after rituximab.

~~Whilst most studies to date have employed rituximab in patients resistant to other therapies in some centres it has been used as a first-line intervention in small numbers of patients.Craythorne, 2011 #138;Cho, 2014 #5459~~ In a single case, rituximab was used as a sole agent and complete healing had been achieved 6 weeks after starting treatment.[106]

c. Dose

Initial studies employed a dosing regimen derived from the treatment of lymphoma patients, using four weekly infusions of 375 mg/m^2.[105] A comparison of repeated weekly treatments of

375 mg/m^2 suggested that pemphigus patients who received three or more infusions demonstrated more rapid complete remission of disease compared with those who only received one or two infusions (149 vs. 443 days) and lower levels of relapse (0% vs. 67%).[107]

More recently, an alternative regimen has been introduced, based on that employed in the treatment of rheumatoid arthritis (RA). Two infusions of 1 g rituximab, 2 weeks apart, has now been shown to be effective in retrospective[108,109] and prospective[45,110] studies. Modified protocols have been used, but data suggests the 'low dose' RA protocol (2 x 0.5 g infusions) has a lower response rate and shorter time to relapse than the standard RA protocol.[111]

Comparison of the standard RA and lymphoma protocols have failed to show consistent superiority of either one. Two studies reported no significant differences,[104,111] although there was a trend to better outcomes in the lymphoma protocol-treated patients in the study by Wang *et al.*[104] In their analysis, Ahmed *at al.* showed significantly better clinical responses in the RA protocol-treated patients but with higher relapse rates (non-significant). In terms of cost, the RA protocol is less expensive, both in terms of drug cost and the associated expense of requiring two rather than four intravenous infusions. Lower–dose treatment (500 mg/twice weekly) has been studied and reported to be effective[112,113] though this approach, may be associated with poorer response and increased rates of relapse.[111,114] Lower-dose rituximab (500 mg) has been used to control relapse following successful treatment with a standard 1 g x 2 induction regimen.[115]

In a single report of resistant oral pemphigus rituximab has been used intralesionally.[116]

d. Combination with other therapies

~~Whilst rituximab has been used as a first-line drug either alone or with corticosteroids by several groups,Ahmed, 2016 #5552;Ingen-Housz-Oro, 2015 #5803;Cho, 2014 #5459;Craythorne, 2011 #138 further studies to define the risks and benefits of this approach are required before it can be recommended as routine management.~~ In general, rituximab has been used as part of combination therapy including systemic corticosteroids together with cytotoxic immunosuppression, or as an adjunct to treatment with IVIG[117] or immunoabsorption.[118-120] Of 372 PV patients who received rituximab reported in the study by Ahmed *et al*., 79% to 97% were treated concomitantly with adjuvant corticosteroids and/or immunosuppressants (59% to 69% with both).[103] ~~One~~ Two studies ~~have~~ employed rituximab together with prednisolone alone: one study of~~in~~ 42 patients to good effect.[121] and a RCT with 46 newly diagnosed patients (38 PV) resulting in complete remission off treatment in 89% of patients.[45] At present, there is insufficient comparative data to indicate which of these approaches is preferable, either from the perspective of efficacy or adverse effects.

Adjuvant systemic immunosuppressive drugs can be continued with concomitant use of rituximab but dose reduction should be considered to decrease the risk of infections and other adverse effects related to immunosuppression.

e. Novel anti-CD20 agents

A number of novel anti B-cell antibodies are currently in development,[122] though to date only one has been reported to have been used in a patient with pemphigus. Veltuzumab (a humanised anti-CD20 antibody) was used as two subcutaneous injections 2 weeks apart in

a patient with severe pemphigus that was refractory to conventional immunosuppression and several cycles of rituximab.[123] Complete remission resulted and was sustained for 2 years, at which point the patient was retreated, again with induction of remission. Whilst rituximab resistance is rare, such novel agents will undoubtedly be of benefit in some patients and may also be more convenient as a result of the subcutaneous route of administration.

Summary

The superior efficacy of rituximab and short-term corticosteroids compared to corticosteroids alone has been demonstrated in a single unblended RCT of newly diagnosed patients with pemphigus. There is also evidence that rituximab is an effective treatment in treatment-resistant disease and in most of these cases has been given in combination with standard immunosuppression. Rituximab is effective for all forms of pemphigus. and in most cases has been given in combination with standard immunosuppression in treatment-resistant cases. Because of its long-lasting effect, cost and the associated risk of infection, currently its use should be reserved for those patients intolerant of or with disease refractory to conventional corticosteroids together with adjuvant immunosuppression. The 2 x 1 g RA dosing protocol is preferred due to cost considerations with similar efficacy to the lymphoma protocol.

14.34 Cyclophosphamide

a. Introduction

Cyclophosphamide treatment regimens in PV vary from daily oral administration to fortnightly or monthly pulses, or a combination of these.[124] Large, comparative trials examining differing doses and regimens are lacking in PV. However, it is interesting to note that studies analysing pulsed intravenous and daily oral cyclophosphamide therapies in the treatment of vasculitis suggest equal efficacy, but with a lower cumulative dose and rate of complications for pulsed treatment[125,126] though the risk of relapse may be higher.[126,127] Guidelines produced for the treatment of ANCA-associated vasculitis also recommend discontinuation of cyclophosphamide, both oral and intravenous, after 3-6 months with transfer to an alternative maintenance therapy, azathioprine or methotrexate, because of the risk of haemorrhagic cystitis, cancer and infertility associated with prolonged exposure to cyclophosphamide. The recommended total duration of cyclophosphamide treatment in this context is up to a maximum of 6 months.[128]

b. Oral cyclophosphamide (Strength of recommendation D, Level of evidence 3)

Early studies reported corticosteroid-sparing effects of cyclophosphamide at doses of 50 to 200 mg/day in case series of up to six patients.[129-133] Prolonged remission with cessation of all therapy was observed in some cases.[130] In a retrospective case series including 20 patients with PV who had failed or were intolerant to azathioprine or mycophenolate mofetil, or had severe PV, cyclophosphamide 2 to 2.5 mg/kg with prednisolone, initially at 1 mg/kg/day, led to remission on minimal prednisolone doses (less than 12.5 mg/day) in 85% of patients.[134] A larger retrospective study included 51 patients treated with cyclophosphamide 100 mg/daily (1.1 to 1.5 mg/kg) and prednisolone 100 mg/daily (1.1 to 1.5 mg/kg) compared with prednisolone alone (n=20) or combined with azathioprine (n=16) or ciclosporin (n=14). The time to clinical and immunological remission was significantly shorter in the cyclophosphamide arm, with lower cumulative corticosteroid doses, suggesting cyclophosphamide is more effective than prednisolone alone and is superior to azathioprine and ciclosporin.[94] However, in an earlier study superiority was not demonstrated: the efficacy

of prednisolone (40 mg/day) alone was compared with prednisolone/cyclophosphamide (100 mg) and prednisolone/ciclosporin (5 mg/kg) in 28 patients with oral pemphigus.[27] There was no significant difference in the duration to achieve remission or in relapse rates between the three groups but cyclophosphamide and ciclosporin were given for a brief period of only 2 to 3 months.[27] Treatment failure for oral cyclophosphamide has been defined by international consensus as failure to achieve disease control after 3 months of treatment at 2 mg/kg/day.[47]

Summary

Oral cyclophosphamide 1 to 2 mg/kg could be considered as an alternative to azathioprine or mycophenolate mofetil. Due to concerns about its toxicity, it is best reserved for patients with recalcitrant or severe PV.

c. Intravenous cyclophosphamide (Strength of recommendation B, Level of evidence 2+)

i. Pulsed intravenous cyclophosphamide with dexamethasone or methylprednisolone

This refers to the intermittent administration of high doses of intravenous corticosteroids and cyclophosphamide, usually three daily doses of dexamethasone (100 mg) or methylprednisolone (500 to 1000 mg) and a single dose of cyclophosphamide (500 mg) given monthly. Doses and frequency are arbitrary.

Dexamethasone–cyclophosphamide pulse (DCP) therapy for PV, first described in 1984 by Pasricha *et al.*,[135] is widely used in India for all types of pemphigus. The originally described regimen comprises four phases: phase 1; monthly intravenous dexamethasone 100 mg on three consecutive days with 500 mg intravenous cyclophosphamide on day 2. Low-dose daily oral cyclophosphamide (50 mg) is administered between pulses. Pulsing is continued until clinical remission and followed by a consolidation phase of a further six DCP courses (phase 2). Oral cyclophosphamide is then continued alone (phase 3) and if there are no relapses after 1 year, all treatment is withdrawn (phase 4). Minor modifications have been made to the regimen, including extending phase 2 to 9 months, reducing phase 3 to 9 months and the addition of daily oral corticosteroids if needed during phase 1.[136] Using the original regimen, 81% (346/425) of pemphigus patients were in remission and had been off all therapy for at least 2 years, 74% (313/425), for more than 5 years.[136] Four percent of patients died during treatment. Using the modified regimen, 86% (106/123) pemphigus patients had completed treatment and had been off-therapy for at least 2 years, 50% (62/123) for more than 5 years. The mortality rate was 2%.

Many other retrospective case series describing the encouraging results of this treatment approach have been published from both Indian centres[137-143] and from other countries around the world including Iran, South Africa, the UK and Serbia.[144-147] In one study, 100% of 32 PV patients completed the regimen and were off treatment, in remission.[138]

Advocates of the DCP regimen claim relative freedom from corticosteroid side effects but 20% to 85% of menstruating females developed amenorrhoea;[145,147-149] azoospermia in men was also noted. Haemorrhagic cystitis occurred in 0.6%[149] and pituitary-adrenal suppression in 55% (17/33) of patients.[150]

ii. DCP regimen compared with oral corticosteroids

DCP therapy has not been tested rigorously against other treatment protocols in controlled trials but one study has compared the 6% mortality achieved in 50 patients (45 PV) on DCP therapy with an estimated 25% to 30% mortality in historical cohorts on conventional corticosteroid therapy at the same institute.[137] More recent studies also indicate an advantage of combining pulsed cyclophosphamide with conventional corticosteroids compared with corticosteroids alone; neither used DCP therapy. In a controlled, open-label study, described in section 18.1, the addition of intravenous pulsed cyclophosphamide 1g monthly for 6 months, then every 2 months, to conventional oral prednisolone resulted in significantly lower cumulative corticosteroid dose at 1 year.[53] Similarly, in a randomized, prospective unblinded trial, 60 PV patients were randomized to receive prednisolone 1 mg/kg/day with or without monthly intravenous cyclophosphamide 15 mg/kg for 1 year. There were no significant differences in the two treatment arms but many outcomes tended to be better in the arm which included pulsed cyclophosphamide, with reduced relapse rates and cumulative corticosteroid doses.[58]

iii. DCP regimen compared with alternative pulsing protocols

One study has compared DCP therapy with an alternative pulsing protocol: in a prospective, randomized open-label trial, 28 PV patients received either DCP therapy or conventional oral prednisolone 1.5 mg/kg plus monthly cyclophosphamide pulses 15 mg/kg. Most efficacy parameters were similar although the time to achieve remission was significantly shorter in the oral prednisolone plus 15 mg/kg cyclophosphamide arm.[79] However, the period of study was 1 year only.

iv. Comparison of pulsed cyclophosphamide with other adjuvant drugs

Modified DCP regimens used in several trials have failed to demonstrate consistent superiority over other corticosteroid/adjuvant PV treatment regimens. Studies comparing pulsed cyclophosphamide with azathioprine and mycophenolate mofetil are summarised in section 18. In summary, three trials have compared azathioprine with pulsed cyclophosphamide regimens: one RCT showed no significant differences;[70] a non-randomized trial favoured pulsed cyclophosphamide which showed a lower cumulative corticosteroid dose although efficacy was similar;[72] a single-centre RCT showed lower cumulative corticosteroid doses in the azathioprine arm which did not reach significance in the authors' analysis but was considered significant in an independent Cochrane review.[52] Pulsed cyclophosphamide has a superior corticosteroid-sparing effect compared with mycophenolate mofetil.[52,53]

v. Dose

The dose of intravenous cyclophosphamide most commonly reported for the treatment of PV is a fixed dose of 500 mg monthly but this is arbitrary and is often combined with 50 mg/day oral cyclophosphamide. Three studies have given 15 mg/kg intravenous cyclophosphamide monthly combined with conventional oral corticosteroids and without daily oral cyclophosphamide.[58,79,81] In another, a fixed dose of 1 g intravenous cyclophosphamide monthly was given, without daily oral cyclophosphamide, and combined with conventional oral corticosteroids.[53] It is common practice to combine intravenous cyclophosphamide with mesna to reduce the risk of haemorrhagic cystitis.[124]

The dose of 15 mg/kg for an intravenous cyclophosphamide pulse is commonly used in the treatment of other severe autoimmune diseases. For example, in remission induction of ANCA-associated systemic vasculitis, pulsed intravenous cyclophosphamide 15 mg/kg (maximum dose 1500 mg) is given initially every 2 weeks, reducing to every 3 weeks and continued for a maximum of 6 months.[128]

Summary

There is some evidence that pulsed cyclophosphamide therapy may reduce cumulative corticosteroid dose. There is no consistent evidence that it is more effective than other adjuvant drugs so in view of concerns about long-term toxicity and the practical disadvantages of administering regular intravenous treatment, it is best reserved for severe or recalcitrant cases of PV.

14.~~12~~5 Intravenous immunoglobulin (IVIG) *(Strength of Recommendation B, Level of Evidence 2++)*

Many reports have suggested the utility of IVIG in patients with PV[151-154] and a recent double–blind, placebo controlled study in 61 patients has confirmed this in a robust way.[155] PV patients treated with a single cycle of IVIG (either 1g/kg or 2g/kg divided over 5 days) did significantly better, measured according to the need for additional treatment, than those treated with placebo and a dose-response effect was demonstrated. Clinical improvement was measured objectively and seen by day 8 in the higher-dose treatment arm. In addition, a significant fall in desmoglein antibody titres was demonstrated in both treatment groups with no fall in the placebo group. A placebo-controlled crossover trial of IVIG in a single patient also confirmed its efficacy, with significantly improved disease activity scores and lower indirect immunofluorescence titres and desmoglein 1 and 3 antibody levels.[156]

In pemphigus, IVIG is generally used at high dose, typically 2g/kg in divided doses over several days, together with corticosteroids with or without cytotoxic immunosuppressive agents such as azathioprine or mycophenolate mofetil. Treatment is given at monthly intervals and may need to be prolonged for continued effect. Thus, multiple treatments will be needed if used to maintain remission. IVIG seems to act by increasing catabolism of pathogenic antibodies.[157,158] It is generally well tolerated[154] and has the attraction over other adjuvant therapies that it does not increase the risk of infection Intravenous immunoglobulin has been used to treat pemphigus in pregnancy[159] and in children.[160]

Whilst uncommon, adverse effects of IVIG do occur, including headache and aseptic meningitis and anaphylaxis which is a particular risk in patients who are IgA-deficient.

Summary

IVIG could be considered as maintenance treatment in patients with refractory disease unresponsive to other adjuvant drugs. In view of reports of a rapid action in some cases, it may also be used to help induce remission in patients with severe PV while slower-acting drugs take effect. IVIG should be considered as part of the acute management of severe or widespread pemphigus and patients who are at particularly high risk of infection.

14.~~5~~6 Methotrexate *(Strength of recommendation D, Level of evidence 3)*

Methotrexate has been used as an immunomodulatory and corticosteroid-sparing agent in a variety of skin diseases. Studies from the late 1960s and early 1970s[14,161-163] attributed high morbidity and mortality to methotrexate and hence it fell out of favour for its adjuvant use in PV. Three of four patients cited in one report died, but high doses of methotrexate had been used (125 to 420 mg/week) in combination with 40 to 240 mg of prednisolone a day.[14] There have been no controlled trials evaluating the role of methotrexate in the treatment of PV.[162-166]

A retrospective review of 116 patients with PV revealed clinical improvement in 83% (96/116) when methotrexate was used in doses between 10 to 50 mg/week, in combination with corticosteroids. Thirteen patients did not improve, two had it discontinued for unknown reasons, and five died from causes unrelated to methotrexate therapy. Of the responders, 14 patients were clear at a mean of 2.6 years (range 3 months to 18 years) after discontinuation of all systemic therapy.[167]

Two retrospective studies have shown a corticosteroid-sparing effect with the use of methotrexate in PV. In a 25-year survey of 53 patients treated with methotrexate and systemic corticosteroids, there was a 50% reduction in the dose of corticosteroids[168] and in the second study, prednisolone (mean dose prior to treatment with methotrexate 20 mg/day; range 3 to 40 mg) was discontinued in six of nine patients.[169]

In 2012, a retrospective review of methotrexate use in PV reported its effectiveness in moderate-to-severe cases as an adjuvant to systemic corticosteroids. A pre-determined severity score was used by the authors, which included the number of erosions, percentage of body surface involved and the dose of prednisolone used. A total of 30 patients were identified and used methotrexate 15 mg/week. Of the 25 patients described as severe or moderate in the study, 84% (21/25) improved their severity score within 6 months ($p = 0.00001$). Only 13% (4/25) experienced side effects. The dose of prednisolone was reduced (range 2.5 to 85 mg) in 23 patients (76.6%) and in 21 patients (70%) the decrease was 50% or more.[170]

A retrospective review by Tran *et al* [171] on the adjunctive use of methotrexate in patients with PV has demonstrated its effectiveness as a corticosteroid-sparing agent; 23 patients with PV were treated with methotrexate, of which 21 (91%) experienced improvement (as measured by reduction in the prednisolone dose). Sixteen patients (70%) were eventually weaned off prednisolone completely. The mean dose of methotrexate used in this study was 18.9 mg/week (range 15-25 mg/week).

Summary

Given the limitations of the data available, it would be difficult to recommend methotrexate as a first-line agent in the treatment of PV.[172] Methotrexate could be considered as an adjuvant drug if more established drugs cannot be used or have failed. International consensus has defined treatment failure as persistent disease despite methotrexate 20 mg/week for at least 12 weeks.[47]

14.~~8.~~7 Dapsone *(Level of evidence 1-)*

Dapsone has been reported to be beneficial as an adjuvant drug in several case reports of PV.[173-177] However, in three of these cases, it was started either with or shortly after prednisolone and in two cases it was started after the long-standing prednisolone was increased to high doses. Therefore, it is difficult to be certain if dapsone had a significant role if any.

In a case series, five of nine PV patients in the maintenance-phase of treatment and who had been unable to reduce their prednisone dose below 15 mg/day or more, experienced a mean (±SEM) drop of 67% (±7.1%) in prednisone dose after 4 months of maximal dapsone treatment and an 84% (±3.5%) drop in prednisone dose after 8 months of dapsone treatment.[178]

There has been one double-blind, placebo-controlled RCT undertaken to look for a potential corticosteroid-sparing effect of dapsone. Nineteen PV patients on maintenance treatment with corticosteroids and/or immunosuppression were randomized to additional dapsone (n=9) vs. placebo (n=10). The primary outcome measure was reduction of prednisolone to 7.5 mg daily for at least 30 days within 1 year of achieving the maximum dapsone dose (150 to 200 mg/day). The results were based upon an intention-to-treat analysis and did not show a statistical difference, i.e. 56% (5/9) of dapsone group were treated successfully, three failed treatment and one left the study. Among the placebo group 30% (3/10) were treated successfully, 57% (4/7) of those that failed treatment were treated with dapsone and in 75% (3/4) of those it was successful. Among those that completed the dapsone trial, 73% (8/11) vs. 30% (3/10) placebo showed a corticosteroid-sparing effect with dapsone. However, the study numbers are very small and at best may only show a slight trend for a corticosteroid-sparing effect with dapsone.[77]

Summary
There is weak evidence to suggest dapsone may have a corticosteroid-sparing effect. Larger placebo-controlled RCTs are needed.

14.~~7.~~8 Tetracyclines/nicotinamide *(Level of evidence 3)*

Tetracyclines have been used in the treatment of PV, with or without nicotinamide, in varying combinations. Sixteen patients were given nicotinamide 1.5 g and tetracycline 2 g daily. In 12, no systemic corticosteroids were given and of these, three cleared and three improved.[179,180] Of the four patients given additional prednisolone, there was clearance in one, partial improvement in two and no response in another.[179]

Thirteen hospitalized patients with PV were given tetracycline 2 g daily for a month followed by 1 g a day for the next 4 weeks in combination with oral prednisolone. They had a faster response rate and required lower doses of prednisolone compared with seven historical corticosteroid-treated controls.[181]

Two studies using minocycline 50 to 200 mg/day as an adjuvant drug reported improvement and a corticosteroid-sparing effect in 54% (7/13) of patients.[182,183]

Summary

Tetracyclines, with or without nicotinamide, are not widely used for the treatment of PV and evidence of their corticosteroid-sparing role is weak, but they could be considered as adjuvant treatment, perhaps in milder cases of PV.

14.9. Sulfasalazine and pentoxifylline *(Level of evidence ~~1~~ 2)*

A double-blind, placebo-controlled clinical trial in 64 PV patients was carried out to ascertain the value of sulfasalazine (SSZ) and pentoxifylline (PTX) as an adjuvant therapy for PV. Patients were not randomized. The drugs were chosen as low-cost, anti-tumour necrosis factor agents. All patients received standard pulsed therapy with intravenous corticosteroid (500 mg on 5 consecutive days) and pulsed cyclophosphamide (on day 1) in a 2- to 4-weekly cycle with oral cyclophosphamide (100 mg/day) and oral corticosteroid (60 mg/twice weekly) between the cycles. In addition, group 1 (n=42) were treated with oral SSZ 500 mg/twice daily and PTX 400 mg/twice daily for 8 weeks while group 2 (n=22) received a placebo. The serum level of TNF-α was higher statistically in both groups of patients than in the healthy individuals. There was a statistically significant decrease in the serum levels of TNF-α in patients in group 1 compared with those in group 2 at 6 and 8 weeks. There was also a rapid clinical improvement in patients in group 1 compared with those in group 2.[184]

Summary

There is some evidence to support the use of PTX and SSZ as adjuvant therapy in the treatment of PV but further studies are required

14.10. Chlorambucil *(Level of evidence 3)*

Like cyclophosphamide, chlorambucil is a nitrogen mustard alkylating agent. Since the last guidelines were compiled, there have been no new reports of the use of chlorambucil in PV. The biggest series, published in 2000, involved seven patients with PV who had failed to respond to other corticosteroid and immunosuppressants. They were given oral chlorambucil 4 mg/day, titrated upwards according to clinical response. There was improvement or remission in five patients and a corticosteroid-sparing effect was noted. A fall in IIF titres was reported in three of four cases.[185] The lack of bladder toxicity with chlorambucil is an advantage compared to cyclophosphamide.

Summary

Chlorambucil could be considered as an adjuvant drug if more established options cannot be used but there are limited data to support its use.

14.411 Gold *(Strength of recommendation D, Level of evidence 3)*

Gold is a historical treatment, rarely used now in the treatment of PV ~~nowadays~~. Most studies have used intramuscular gold, given as sodium aurothiomalate initially at a dose of 50 mg/week intramuscular injection (im) if test doses were tolerated. It was used successfully as monotherapy in five patients with an associated fall in IIF titres.[186,187] However, it has been used more commonly as an adjuvant drug and corticosteroid-sparing effects are reported. Penneys *et al.* reported a series of patients receiving gold for up to 4 years with 14 of 15 patients responding. Eight achieved remission off-treatment after a mean of 21 months, 7 achieved remission on treatment and one stopped due to side effects.[188] In a retrospective review of 26 patients treated with gold over 10 years, a response was seen in

62% and complete remission off-treatment had occurred in four patients. Toxicity was seen in 42%. The average dose of prednisolone was reduced from 55 mg/day pre-gold to 9 mg/day at the end of the study.[189] A more recent study used gold as an adjuvant therapy in 13 patients with prednisolone doses ranging from 7.5 to 100 mg. The addition of 50 mg im gold was felt to be beneficial as 7 patients went into complete remission and 4 were able to reduce prednisolone doses.[190]

Significantly, there are also case reports implicating gold as a trigger for pemphigus. Gold compounds contain a thiol group which has previously been implicated in drug-induced pemphigus. Lo Schiavo *et al.* reported a convincing case of gold-induced pemphigus in a patient with rheumatoid arthritis, with complete resolution on withdrawal of gold.[191]

Summary

Gold is now a historical treatment in most developed healthcare systems. It could be considered as an alternative to more established adjuvant drugs if they cannot be used or are unavailable. However, the lack of randomized trial data makes the magnitude of an effect uncertain and there is a risk of gold acting as a disease trigger.

14.~~6.~~12 Ciclosporin *(Level of evidence 1-)*

There are a number of case reports suggesting that ciclosporin is a useful adjuvant with corticosteroid-sparing effects in PV.[64,192-194] However, a small prospective single-centre RCT of 33 patients comparing oral methylprednisolone 1 mg/kg alone vs. methylprednisolone with ciclosporin 5 mg/kg found no statistically significant difference in outcome measures such as time to healing, complete remission rate and cumulative corticosteroid dose. More side effects were encountered in the ciclosporin group during a mean follow-up period of 5 years.[195] There were no deaths and 10 patients (five from each group) were in complete remission, off all therapy, while the others were taking an average of prednisone 2.5 mg/day.[195] Olszewska *et al.* reported a retrospective series of 101 patients with PV treated with prednisolone alone (n=20) or in combination with adjuvant immunosuppressants, including azathioprine (n=16), ciclosporin (n=14) and oral cyclophosphamide (n=51). Cyclophosphamide plus prednisolone was significantly better at inducing remission than prednisolone alone. Ciclosporin did not add any significant benefit. The proportion remaining relapse-free 5 years after discontinuation of treatment was lowest in the ciclosporin group, at 43%, and highest in the cyclophosphamide group at 69%.[94]

Summary

On the basis of current evidence, ciclosporin cannot be recommended as an adjuvant drug in PV.

15.0 PLASMA EXCHANGE/PLASMAPHERESIS *(Strength of Recommendation D, Level of Evidence 3)*

Plasma exchange has been used for many years in the management of antibody-mediated autoimmune disease, including pemphigus. Thus, multiple case reports and small case series have reported clinical benefit, short-term falls in IIF titres and a corticosteroid-sparing effect of plasma exchange.[196-208] In general, these were problematic patients with either corticosteroid side effects, poorly controlled disease on conventional therapy or life-threatening disease. However, a randomized study of patients with newly diagnosed pemphigus treated with oral corticosteroids with or without additional plasma exchanges

failed to demonstrate any additional clinical benefit of plasma exchange. Cumulative corticosteroid doses and changes in IIF titre in the two groups were similar. Furthermore, there were four deaths from sepsis in the plasma exchange group.[209] In the cases reported that have been treated successfully, plasma exchange has been combined with both corticosteroids and immunosuppressive drugs - it is thought that the latter is necessary for sustained clinical effect in order to prevent rebound production of autoantibodies stimulated by the plasma exchange.[196,199,204,205,210-213] IVIG has been reported to have a similar action and has been used successfully in combination with plasmapheresis.[214]

Plasma exchange is not without adverse effects as, in addition to pathogenic immunoglobulins, other important plasma proteins are removed such as clotting factors that can result in coagulation defects.[215]

Summary
Plasma exchange cannot be recommended as a routine treatment option in newly presenting patients with pemphigus but may be considered in refractory cases if combined with corticosteroids and immunosuppressant drugs.

16.0 EXTRACORPOREAL PHOTOPHERESIS *(Strength of Recommendation D, Level of Evidence 3)*

Extracorporeal photopheresis is known to have immunomodulatory effects[216] and has been used in small numbers of patients with pemphigus;[217-222] there are no RCTs. In a recent case series, 8 patients with pemphigus were treated with 2 to 6 cycles of extracorporeal photopheresis, resulting in complete remission in all but one case. Steroid doses could be tapered in all treated patients.[223]

Summary
Extracorporeal photopheresis could be considered in recalcitrant cases of PV where there has been failure to improve with more conventional therapy.

17.0 IMMUNOADSORPTION *(Strength of Recommendation D, Level of Evidence 3)*

Immunoadsorption is an extracorporeal apheresis technique in which patient serum is passed over a matrix that selectively adsorbs immunoglobulin. Consequently it removes circulating pathogenic antibodies and is widely used in transplantation medicine.[224] Immunoadsorption was first used in the management of pemphigus in 1999 and several case series and reports have evidenced its utility since then.[225-227] Various matrices have been used including Staphylococcal Protein A and tryptophan.[226-228]

Immunoadsorption has been used together with rituximab[118,119] and other adjuvant immunosuppressive agents.[120,226,227] It is effective in difficult-to-treat disease and represents a rational approach in the reduction of circulating pathogenic antibody levels when combined with treatment directed at suppressing new antibody formation such as rituximab.[118] Daily treatment over 3 consecutive days can result in falls in desmoglein antibody levels of up to 95%.[228] As yet, however, there is no consensus on an optimal matrix or regimen and the use

of immunoadsorption should be reserved for the treatment of patients resistant to or intolerant of other approaches.

Summary

Immunoadsorption could be considered in recalcitrant cases of PV where there has been failure to improve with more conventional therapy.

18.0 COMPARISONS OF SYSTEMIC ADJUVANT DRUGS

18.1 Azathioprine and mycophenolate mofetil

In an unblinded multicentre RCT, 40 patients with pemphigus (33 PV and 7 PF) were randomized to receive mycophenolate mofetil (1g twice daily, n=21) or azathioprine (2mg/kg/day, n=18), both in combination with a standardized corticosteroid regimen (methylprednisolone, initial dose 2mg/kg/day); they were followed-up for 2 years. There were no significant differences in efficacy, adverse event profile or cumulative corticosteroid dose between the two arms. There was a trend towards azathioprine achieving a faster clinical remission, although more patients achieved remission with mycophenolate mofetil 95% (20/21) after a mean of 91 days vs. azathioprine 72% (13/18) after a mean of 74 days, and there were fewer grade 3 or 4 adverse events with mycophenolate mofetil (19% vs. 33% for azathioprine). However, the study was small with wide confidence intervals.[71]

In a further unblinded single-centre RCT, mycophenolate mofetil and azathioprine were compared as adjuvant drugs, in addition to pulsed cyclophosphamide.[53] A total of 120 PV patients were randomized to four groups of 30 patients: prednisolone alone (initial dose 2 mg/kg/day); prednisolone plus azathioprine (2.5 mg/kg/day for 2 months followed by 50 mg daily); prednisolone plus mycophenolate mofetil (2 g/day); prednisolone plus intravenous cyclophosphamide (1g monthly for 6 months, then 1g every 2 months). A total of 111 patients completed the 1-year follow-up. Efficacy and adverse events were similar in all four arms but the cumulative corticosteroid dose was significantly higher in the prednisolone-only arm compared with the combined adjuvant groups. The lowest cumulative dose was in the azathioprine arm (azathioprine <intravenous cyclophosphamide <mycophenolate mofetil) and there was a significant difference between the azathioprine and mycophenolate mofetil arms, favouring azathioprine.

In a Cochrane systematic review[52] of these two studies comparing mycophenolate mofetil with azathioprine,[53,71] the combined data showed that azathioprine had a significantly better corticosteroid-sparing effect, measured as cumulative corticosteroid dose. However, they concluded that the Beissert *et al*. study[71] showed that mycophenolate mofetil was more effective than azathioprine at achieving a higher proportion of patients with disease control.[52]

18.2 Azathioprine and oral cyclophosphamide

A retrospective study of 101 patients included 20 treated with prednisolone alone and three groups treated with combinations of prednisolone and immunomodulatory drugs: 51 treated with cyclophosphamide 100 mg daily (1.1 to 1.5 mg/kg) 16 with azathioprine (100 mg daily initial dose) and 14 with ciclosporin (2.5 to 3 mg/kg/day). The time to clinical remission was significantly shorter in the cyclophosphamide arm compared with the other three groups. The cyclophosphamide group also had a lower cumulative corticosteroid dose and a shorter time

to immunologic remission (no detectable antibodies). This study suggests that cyclophosphamide plus prednisolone is more effective than prednisolone alone and is superior to azathioprine plus prednisolone and ciclosporin plus prednisolone.[94]

18.3 Azathioprine and intravenous cyclophosphamide

In a small, multicentre RCT of 22 pemphigus patients (16 PV) a regimen of oral methylprednisolone (initial dose 2 mg/kg) and azathioprine (2 to 2.5 mg/kg) was compared with a DCP regimen. The DCP regimen comprised pulses of 3 x 100 mg intravenous dexamethasone and 500 mg intravenous cyclophosphamide day 1, repeated every 2 to 3 weeks initially, dropping down in frequency to every 6 weeks. Oral cyclophosphamide 50 mg daily was given between pulses but stopped after 6 months. Cyclophosphamide pulses were stopped when there was no relapse at 6 weeks from the last dose, but dexamethasone pulses were continued every 12 weeks. Patients were followed up for 2 years and there were no significant differences in either efficacy or adverse effects in the two treatment arms.[70]

Another study has compared a modified DCP regimen (each course included 1000 mg intravenous methylprednisolone for 4 days plus 500 mg intravenous cyclophosphamide for 1 day) with oral prednisolone (1 to 2 mg/kg initial dose) plus azathioprine (100 to 150 mg/ daily). Only 3 monthly pulses were given with oral cyclophosphamide 50 mg/daily and oral prednisolone, initially 30 mg/daily, between pulses. It was not randomized, with 72 patients in the pulse arm and 51 in the control arm. Most outcome measures were similar in both groups although at 1 year, cumulative corticosteroid doses and weight gain were significantly greater in the azathioprine arm suggesting superiority of the DCP regimen compared with oral prednisolone and azathioprine.[72]

In the non-blind single centre RCT which recruited 120 PV patients and is described in section 18.1, efficacy and adverse effects were similar in the pulsed cyclophosphamide and azathioprine arms.[53] Cumulative corticosteroid dose was lower in the azathioprine arm but it was not significantly different to the cyclophosphamide arm. However, a Cochrane systematic review of this data indicated the difference in cumulative corticosteroid dose was significant, favouring azathioprine as an adjuvant drug.[52]

18.4 Intravenous cyclophosphamide and mycophenolate mofetil

Only one study comparing cyclophosphamide pulses with mycophenolate mofetil has been described (see section 18.1). In this study 30 PV patients were recruited to each arm. There were no significant differences in efficacy or adverse events.[53] Both arms showed a corticosteroid-sparing effect, measured as cumulative prednisolone dose, but the difference between the cumulative corticosteroid dose in both arms was reported by the authors as not significant using ANOVA. A Cochrane systematic review of this data indicated the difference in cumulative corticosteroid dose was significant, favouring pulsed cyclophosphamide as an adjuvant drug.[52]

19.0 TOPICAL THERAPY FOR THE SKIN *(Level of Evidence 1-)*

PV is largely managed with systemic therapy. However, high-quality skin care is essential and adjuvant topical therapy, including topical corticosteroids, may be of additional benefit,

although there are no controlled studies to confirm this. Rarely, patients with mild disease, particularly if confined to the mucosal surfaces, can be managed on topical therapy alone. Huilgol *et al.* have reviewed topical therapy for pemphigus and pemphigoid in detail.[229,230] Topical tacrolimus ointment 0.1% in combination with systemic treatment has been reported to heal recalcitrant facial erosions.[231] A small, randomized double-blind clinical trial (11 patients, 62 lesions) demonstrated significant benefit of pimecrolimus 1% cream over placebo for the healing of cutaneous erosions. The patients were also receiving systemic immunosuppression.[232] Other small randomized trials treating cutaneous lesions have suggested benefit from pilocarpine gel 4%,[233] nicotinamide gel 4%[234] and epidermal growth factor(10 µg/g) in 0.1% sulfadiazine cream.[235] Scalp lesions can be particularly persistent and are often covered in thick crust rather than being eroded. Soaking the crust in emollient or oil followed by gentle washing to remove the crust allows topical corticosteroids to penetrate better. Avoid corticosteroid scalp preparations in an alcohol base because they sting; use lotions or creams instead. Nasal lesions can be managed with topical corticosteroid nasal preparations such as fluticasone propionate nasules 400 micrograms twice daily.

20.0 ORAL MANAGEMENT *(Strength of recommendation D, Level of evidence 3)*

Oral lesions in PV are characterized by painful ulceration involving any surface of the oral cavity. The buccal mucosa, soft palate, lips and tongue are most frequently affected. Painful erosions on the gingival margins may inhibit tooth brushing resulting in an accumulation of plaque. This compounds the pain and inflammation. Furthermore, patients with PV have a worse periodontal status than seen in matched controls.[236,237]

a. Topical corticosteroid preparations

These are frequently used as adjunctive therapy. However as most patients are on concomitant systemic therapy evidence for the additional benefit of topical treatments is poor. Nevertheless, topical corticosteroid preparation are often used in patients with mucosal PV and include corticosteroid mouthwashes such as betamethasone sodium phosphate 0.5 mg dissolved in 10 mL of water as a 2-3 minute rinse-and-spit solution 1-4 times a day, flixonase nasules diluted in 10 mL of water twice daily or clobetasol 0.05% ointment mixed in 50% Orabase® twice weekly applied to localised lesions on a dried mucosa. The latter can be mixed together by the patient and stored in the fridge.

b. Tacrolimus

In a split-mouth,(two treatments compared when applied to one or other side of the mouth at the same time) randomized trial over 2 weeks (n=15) the efficacy of triamcinolone acetonide 0.1% paste (Volon-A®) was compared to tacrolimus 0.1% ointment (Protopic®).The degree of mucosal involvement and pain scores were significantly reduced in both treatments compared with baseline but there was no difference between the treatments.[238] Topical tacrolimus, applied twice daily for 4 weeks was beneficial in one case of recalcitrant PV affecting the lips.[239]

c. Topical ciclosporin

There are small numbers of reports indicating that topical ciclosporin is effective for the oral lesions of PV. A 5mL (500 mg) of oral suspension used 3 times a day for 2 months in oral

pemphigus (n=12) recalcitrant to conventional treatment was reported to result in significant improvement in both symptoms and signs of PV.[240]

Ciclosporin mouthwash(100 mg/ml) 5mL used 3 times day was effective within 6 months in a patient with recalcitrant oral lesions for 20 years.[241] Treatment was reduced and the patient was maintained on a once-daily mouthwash for 5 years. In a further three PV patients, 66% (2/3) patients had a clinical improvement.[242] However, topical ciclosporin tastes unpleasant and is relatively expensive.[242]

d. Intralesional triamcinolone

Mignogna *et al.* evaluated the efficacy of perilesional/intralesional triamcinolone acetonide injections in oral PV in addition to conventional immunosuppressive therapy plus topical corticosteroid (n=16) in an open-label trial.[243] In comparison to a group of patients not receiving injections (n=19), the perilesional/intralesional triamcinolone acetonide group achieved a shorter time to clinical remission (126 days vs. 153; not statistically significant) and obtained acceptable compliance with this treatment.

e. Topical prostaglandin E2

Topical prostaglandin E2 applied twice daily in ten patients with oral lesions in PV resulted in complete healing by 3 months in 30% (3/10) PV patients. These had mainly mild disease affecting one mucosal site. A further three patients improved as long as treatment was continued but relapsed within 7-10 days of stopping therapy while 4/10 did not improve. Other treatments had been discontinued 2 weeks prior to the study.[244]

Recommendations for oral treatment

- Maintenance of good oral hygiene is paramount. Use of soft toothbrushes and mild, mint-free toothpaste may be helpful, e.g. paediatric formulations or Kingfisher fennel. Regular, 3-monthly attendance to a dental hygienist is recommended. In addition, use of an antiseptic mouthwash two or three time a week diluted if necessary, may also be helpful. Agents include 1.5% hydrogen peroxide, e.g. Peroxyl® mouthwash, 10 ml twice daily or 0.2% chlorhexidine digluconate mouthwash, e.g. Corsodyl® mouthwash, 5-10 ml twice weekly. Dilution of mouthwashes (50%) may be necessary to reduce discomfort. Barrier preparations such as Gengigel ® mouth rinse or gel or Gelclair ® are also helpful for pain control.

- Use of an anti-inflammatory oral rinse or spray containing benzydamine hydrochloride, e.g. Difflam® oral rinse or spray may be helpful particularly before meals. Anaesthetic preparations, e.g. viscous lidocaine 2% gel may also be helpful.

- Patients are susceptible to oral candida and therefore oral swabs or saliva sampling is helpful at each visit. Use of nystatin oral suspension four times a day for 1 week per month may be helpful.

- For multiple oral erosions, mouthwashes are most practical, for example, soluble betamethasone sodium phosphate 0.5 mg tablet dissolved in 10 mL water may be used up to four times daily, holding the solution in the mouth for about 2 to 3 minutes and reducing the frequency as oral lesions improve. Flixonase nasules (400 µg) similarly

21.0 NURSING CARE

PV has the potential to cause extensive cutaneous erosion, and in very active cases, fragility of normal skin (exhibited by a positive Nikolsky sign). Therefore, careful handling of the skin by specialist dermatology nurses, or other nursing staff familiar with caring for patients with skin failure, is essential. Attention to fluid balance, haemodynamic stability, thermoregulation, prevention of infection, prevention of further skin trauma, pain management, nutritional intake and psychological support is equally important in addition to skin care.[245]

It is recommended that any intact bullae are decompressed by piercing. The blister roof is left *in situ* to act as a biological dressing. A daily blister chart is a useful means of mapping disease progress in the acute phase.[246]

21.1 A guide to blister management:

Anecdotal experience suggests that aspirating blisters causes more discomfort than piercing them. Table 2 summarises the management of blisters for all types of bullous disease including PV and epidermolysis bullosa.

1. Gently cleanse blister with antimicrobial solution, taking care not to rupture
2. Pierce blister at base with a sterile needle, with the bevel facing up. Select a site in which the fluid will drain out by gravity to discourage refilling.
3. Gently apply pressure with sterile gauze swabs to facilitate drainage and absorb fluid.
4. Do not de-roof the blister.
5. After fluid has drained, gently cleanse again with an antimicrobial solution.
6. It may be necessary to apply a~~n atraumatic~~ non-adherent dressing.
7. Some large blisters may need a larger hole to drain

Table 2. Management of blisters

The application of a bland emollient, such as 50% white soft paraffin and 50% liquid paraffin, is recommended to support barrier function,[247] reduce transcutaneous water loss and encourage re-epithelialisation.[248,249] This should be applied to the whole skin including erosions. Avoid products containing irritants and sensitizers. To reduce the shearing forces and pain associated with application of emollients to erosions, a 50:50 aerosolized preparation of white soft liquid paraffin can be used to supplement application of the ointment form. Emollients can be applied directly to the skin or initially to primary dressings.

Potassium permanganate soaks (one Permatab® – 400 mg – in 4 litres of water, i.e. a 1:10,000 solution) may be helpful for wet, weepy erosions. The solution should not be applied for longer than 15 minutes as it becomes ineffective due to oxidation. If practical, soaking in a bath is an effective way of treating large areas. Alternatively, it can be applied by soaking gauze swabs or dressing pads and applying to affected areas. The patient should be counselled regarding temporary skin discoloration. Nails should be covered with white/yellow soft paraffin to help prevent nail discoloration.[250-252]

There is no clear evidence regarding the superiority of any particular dressing in PV, but those used should be non-adherent.[253] The application of an emollient and dressing to eroded areas helps reduce fluid and protein loss, reduces the risk of secondary infection and assists with pain control. A soft silicone mesh dressing, such as Mepitel®, is a suitable primary dressing, and it can be coated (spread) with an appropriate emollient such as 50:50 mix of liquid paraffin and white soft paraffin, or topical antimicrobial if appropriate, prior to applying to the skin. The secondary dressing usually needs to be absorbent, such as a soft silicone foam or other foam dressing, for example Mepilex® or Allevyn®.[253] These dressings can be secured to the trunk or the limbs with soft knitted tube dressings such as Comfifast®.

When dressings are removed, if they have dried onto the skin, they should be soaked off to minimize pain and avoid further damage.[254] There is no evidence regarding the optimal frequency of dressing changes but one should consider the appearance of strikethrough on

the secondary dressing, the need to assess for evidence of infection and the stage of wound healing. In the acute stage, dressings should be changed daily to assess these. It may be appropriate in the later stages of healing to change only the secondary dressing but leave the primary dressing *in situ*, the underlying erosion left undisturbed. Further applications of topical agents can be placed on top of the silicon mesh primary dressing in this situation. Crusts should be removed to promote healing. All pemphigus patients should be nursed on an appropriate pressure-relieving mattress regardless of the degree of skin failure as they are prone to developing pressure areas by virtue of the disease.[255]

Infection and sepsis are a significant risk and a major cause of mortality in PV so vigilance in detecting signs of infection is essential.[256] Infection also increases the risk of scarring. Daily washing with an antibacterial product can decrease colonization. Dressings should be changed using an aseptic technique and patients with extensive erosions barrier nursed. Erosions showing clinical signs of infection should have bacterial and viral swabs sent. It may be appropriate to apply topical antimicrobials for short periods only. Systemic antibiotics should be used if there are local or systemic signs of infection or extending infection of the skin. Local policy should guide the choice of antibiotic agent.

Pain control is essential, and attention needs to be paid both to acute and maintenance (background) analgesia with the ability to provide timely additional short-term boosts when needed, for example with dressing changes. The advice of a pain team may be necessary.

22.0 PEMPHIGUS IN PREGNANCY ***(Level of evidence 3)***

This is a rare occurrence requiring close cooperation between dermatologist, obstetrician and neonatologist. Careful selection and monitoring of immunosuppression during pregnancy is required. Due to the passive transfer of maternal IgG autoantibodies across the placenta, the neonate may be affected by cutaneous erosions. In 2009, Kardos *et al*. published a review of 38 reports describing 49 pregnancies affected by pemphigus.[257] Prednisolone alone was used in 75% (37/49) of the cases at doses between 5 to 300 mg/day. Adjuvant therapies were used in eight patients; azathioprine (n=5), plasmapheresis (n=1), plasma exchange (n=1) and dapsone (n=1). Five neonatal deaths were reported. Twenty (45%) of the neonates had pemphigus lesions at birth with all resolving within 4 weeks either spontaneously or with mild topical corticosteroids. Overall, there seems to be an increased risk of foetal morbidity with gestational PV with higher preterm birth rates and low birth weight. There is no clear increased foetal loss.[258]

The most commonly used treatments for pemphigus in pregnancy are oral corticosteroids. Current evidence suggests that there is no significant increased risk of stillbirth, preterm delivery or congenital malformations from using prednisolone in any disease, though the usual side effects of corticosteroid use will still occur.[258] Both systemic and very potent topical corticosteroids have been linked with intrauterine growth retardation. Corticosteroids should be the first-line systemic agent. The type of corticosteroid used is important since prednisolone is 90% inactivated by the placenta whereas betamethasone and dexamethasone are far less inactivated and could have a greater effect on the foetus.

There are no prospective studies of immunosuppressant therapy for pemphigus in pregnancy. Many systemic immunosuppressive agents including mycophenolate mofetil, methotrexate and cyclophosphamide should be avoided due to known risks to the foetus.

Azathioprine, in combination with corticosteroids, has been used successfully for pemphigus.[257] Whilst there are risks of teratogenicity with azathioprine these are low and azathioprine has been widely used during pregnancy in association with renal transplantation, inflammatory bowel disease and systemic lupus erythematosus.[259]

IVIG is safe in pregnancy. Ahmed *et al.* report eight patients with severe pemphigus in pregnancy. Seven responded well and one developed headaches and stopped treatment; none of the neonates had any erosions.[159] Finally, plasmapheresis has been used successfully although this option is unavailable in many centres.[260]

Rituximab has been used successfully in childhood pemphigus though its effects in pregnancy are uncertain.[261-263] Rituximab is able to cross the materno-foetal barrier and the manufacturers advise against pregnancy for 1 year following rituximab therapy. The drug may affect the developing immune system potentially, and thus, the risks to mother and foetus need to be considered carefully prior to treatment. If a pregnancy is exposed to rituximab the baby should avoid live vaccines for at least the first 6 months of life.[264]

Maternal IgG is excreted in human milk and women should not breastfeed whilst receiving rituximab and for up to 12 months following the last infusion.

Summary

Pemphigus occurring in pregnancy is rare. Data suggests that there is no increased risk of fetal loss although some morbidity is seen especially with respect to low birth weight. Prednisolone alone is the most common treatment. Certain second line treatments have been safely used when needed.

23.0 PEMPHIGUS VULGARIS IN CHILDREN ***(Strength of recommendation D, level of evidence 3)***

Even though PV affects adults predominantly, it can occur in children. A ~~recent~~ review ~~has~~ suggested a further subdivision of this group into childhood PV, referring to disease in children younger than 12 years old, and juvenile PV, affecting adolescents aged between 12 and 18 years.[265] This sub-classification helps delineate the potential adverse effects of medications used in these subgroups. A self-limiting form of PV can occur in neonates born to mothers with PV, due to trans-placental transfer of autoantibodies.

Systemic corticosteroids are the treatment of choice in both childhood and juvenile PV,[67] but children are more susceptible to the potential adverse effects of corticosteroids compared to adults. Growth retardation is the most important adverse effects in children on long-term oral corticosteroids. In both children and adolescents, the height will need to be recorded regularly and expert advice is prudent if high-dose corticosteroids are used long-term.

Regular checks for signs of adrenal suppression are recommended (http://cks.nice.org.uk/corticosteroids-oral#!scenario).[266]

In a series of 33 patients with childhood PV, prednisone was used in 26; with the dose ranging from 12 to 500 mg/day (mean 88.3 mg/day). Other immunosuppressant medications used included gold (n=2), azathioprine (n=6), dapsone (n=4), cyclophosphamide (n=2), ciclosporin (n=1), rituximab (n=2), mycophenolate mofetil (n=1), and IVIG (n=1). Six patients (18.2%) achieved complete recovery and 78.8% (26/33) had partial remission, with minor relapses whilst on maintenance therapy. Of concern was the high rate of serious side effects, with cushingoid features in 65%, growth retardation in 50% and infection in 50%.[267]

Juvenile PV has features similar to adult PV but disruption of biological and social development due to the skin disease raises particular concern during adolescence. The largest series of juvenile PV included 47 patients, with 42 requiring systemic corticosteroids. Corticosteroid-sparing agents used included azathioprine (n=1), intramuscular gold (n=1), dapsone (n=3), cyclophosphamide (n=2), mycophenolate mofetil (n=2), and rituximab (n=3). IVIG was reported in eight patients, for four of whom it was used as monotherapy. All 47 patients responded to treatment, with adverse effects reported in 19%. Infection (8.5%), weight gain (10.6%), and cushingoid appearance (6.4%), were the main side effects, associated mainly with systemic corticosteroids.[67,268] Relative youth may be a positive factor in terms of prognosis and mortality.[268]

There have been only 18 anecdotal reports of the use of rituximab in PV affecting children.[263,269-272] It may have a role in PV affecting children when treatment with systemic corticosteroids and other immunosuppressants have failed to confer any benefit. It has been used as monotherapy or in combination with systemic corticosteroids and other immunomodulatory drugs.

IVIG therapy has been reported to be effective in children with juvenile PV.[273,274] It can be used as monotherapy or in combination with other systemic agents.[268] IVIG is an attractive second-line option for juvenile PV as the risk of thromboembolic events and renal failure are considered to be much less compared to adults.[274]

Summary

The course of PV in children is generally favourable, with a better prognosis compared to adult PV.[263] Due to its rarity, there are no RCTs in the use of systemic agents in this condition. Overall, its treatment after initial systemic corticosteroids is similar to adult regimens and the same adjuvant therapies can be used.

24.0 INDUCED PV

Drugs can trigger pemphigus but this is uncommon. The diagnosis is challenging because drug-induced cases resemble idiopathic pemphigus, there are no clinical or laboratory tests that can distinguish reliably and the latency between starting the drug and disease onset can be several months. Therefore, a thorough drug history is essential, cross-checking against drugs reputed to trigger pemphigus (see Table 3).[275,276] A poor response to standard systemic treatment should also alert to the possibility of drug-induced pemphigus (DIP).

Thiol drugs	Phenol drugs	Non-thiol, non-phenol drugs
Captopril	Cefadroxil	Calcium channel blockers
D-Penicillamine	Rifampicin	ACE inhibitors
Gold	Levadopa	NSAIDS
Carbimazole	Aspirin	Progesterone
Penicillin	Heroin	Glibenclamide
Piroxicam	Phenobarbital	Pyrazolone derivatives

Table 3. Drugs reputed to trigger pemphigus[275,276]

There are three groups of chemical structures which have been suggested to cause drug-induced pemphigus: thiol drugs, which have a sulfhydryl radical; phenol drugs; and non-thiol, non-phenol drugs (see Table 3). PF is the most common pattern of DIP, observed in up to 70% of thiol-induced cases. Non-thiol drugs tend to trigger a PV phenotype. Pruritus is more common in DIP than in idiopathic pemphigus.[275,277] Diagnostic investigations are as for idiopathic pemphigus, with no immunopathological features in routine investigations that differentiate.[278]

Initial management of DIP includes stopping the offending drug, possibly combined with conventional treatment in severe cases to hasten remission. Thereafter, it may follow two courses: the disease may continue in 50% in spite of drug withdrawal (drug-induced pemphigus) whilst the others recover completely (drug-triggered pemphigus).[279] Recovery following drug withdrawal is more likely in thiol-triggered cases. In patients who do not remit upon drug withdrawal, the course and prognosis is similar to idiopathic disease and should be managed as such.

25.0 PATIENT SUPPORT

Patients should be directed towards reputable sources of information and support. A patient information leaflet is available on the BAD website (www.bad.org.uk/for-the-public/patient-information-leaflets). In the UK, the PV Network (www.pemphigus.org.uk) and PEM Friends (UK) (www.pemfriends.co.uk) and internationally, the Pemphigus Pemphigoid Foundation (IPPF, www.pemphigus.org), are organisations providing patient support. Patients with PV may need psychological support to help them cope with coming to terms with a chronic, painful and visible disease or the impact of its treatment, particularly corticosteroids.[280,281] The input of a pain management team may be needed to advise on management of painful skin or mucosal lesions and the advice of a dietician if oral intake is impaired**.**

26.0 FOLLOW-UP AND TAPERING OF TREATMENT

Once remission is induced, there should follow a period of maintenance treatment using the minimum drug doses required for disease control and during which occasional blisters are acceptable. Drug doses should be reduced slowly (see section 12) and patients should remain under follow-up while they remain on therapy. Ultimately, treatment may be withdrawn if there has been prolonged clinical remission. The chances of relapse are reduced if immunofluorescence or ELISA studies are negative, e.g. the risk of relapse is

13% to 46% if DIF is negative, 44% to 100% if DIF is positive; 24% if IIF is negative, and 57% if IIF is positive;[282-284] 25% if desmoglein 3 ELISA is negative, 56% if desmoglein 3 ELISA is positive.[285] In DIF-negative patients, there is some evidence to suggest that relapse is less likely the longer a patient has been in remission on minimal therapy prior to stopping treatment; 46% in all DIF-negative patients, 22% in those in remission for 6 months and 0% with remission of over 12 months.[284] However, DIF can remain positive occasionally in patients who are in remission and off all treatment.[21] A less invasive and relatively simple alternative to DIF on a skin biopsy, in this situation, is DIF on the outer root sheath of plucked hairs.[286] This investigation is not widely available at present.

There is no evidence to guide the order in which treatments are reduced and withdrawn in PV. However, it is common practice to withdraw corticosteroids first,[287,288] to minimize their side effects, whilst maintaining adjuvant immunosuppressants at full dose (see section 12 for guidance on the rate of dose reduction). Thereafter, adjuvant drugs can be tapered slowly if remission is maintained. If complete treatment withdrawal is successful, and the patient remains in complete remission for a prolonged period, discharge to their primary care physician is reasonable but patients and their carers should be warned that PV can recur, in which case they should be referred to secondary care immediately.

27.0 FUTURE DIRECTIONS

As these guidelines illustrate, there is a lack of high-quality evidence supporting the use of many drugs in PV. Even answering the basic question of whether there is benefit in adding adjuvant immunosuppressants to corticosteroids is not clear-cut for most drugs. The answers to these questions will only come from large, multicentre RCTs which would need to be of sufficient length to demonstrate the long-term outcomes that are of relevance in this chronic disease.

The role of biologics and their place in the management of PV is an area of great interest. ~~So far, m~~Most experience comes from treating patients with established disease resistant to standard treatment. ~~.~~ It is interesting to speculate whether using rituximab, or newer anti-CD20 drugs, as a first-line drug in newly presenting, treatment-naïve patients, might offer better long-term outcomes compared with the standard approach of corticosteroids with an adjuvant immunosuppressant. Such potential advantages might offset its additional cost in the long-term. A recent unb~~e~~inded RCT has shown that rituximab combined with prednisolone is more effective than prednisolone only in newly diagnosed patients.[45] Further studies to confirm this result and to compare with corticosteroid/immunosuppressant combinations are awaited.

The development of anti-CD20 drugs that can be self-administered by subcutaneous injection also has the potential to be a very useful step forward. At present, ongoing trials using rituximab and ofatumumab may help answer some of these questions and positive results may lead to formal licensing, making use of these drugs more straightforward. In 2016, NHS England approved routine commissioning of rituximab in the treatment of pemphigus that has failed to respond to systemic steroids together with adjuvant immunosuppressive agents such as mycophenolate or azathioprine (policy available at https://www.england.nhs.uk/commissioning/wp-

content/uploads/sites/12/2013/04/16035_FINAL.pdf), thereby ensuring consistent access and funding across the UK National Health Service in England. This document was produced prior to the recent RCT using rituximab.[45]

Further investment in diagnostic laboratories is needed to enable routine use of tests such as immunoprecipitation to enable more precise diagnosis of pemphigus subtypes leading to better targeted investigation and treatment

28.0 RECOMMENDED AUDIT POINTS

In the last 20 consecutive patients with PV, or all patients seen in the last 12 months (if less than 20), is there clear documentation of:

1. Measurement of baseline parameters prior to starting treatment
   As a minimum this should include:
   - Weight
   - Blood pressure and whether there is a clinical history of hypertension
   - Height (children)
   - Blood glucose and HbA1c and whether there is a clinical history of diabetes
   - Pregnancy test (if appropriate)
   - Full blood count, renal and liver function tests

2. Appropriate investigations to establish diagnosis
   As a minimum this should include:
   - A lesional skin/mucosal biopsy for routine histopathology
   - Perilesional skin/mucosal biopsy for direct immunofluorescence (alternatively, indirect immunofluorescence or desmoglein ELISA if biopsy is not possible)
3. Evidence of appropriate drug monitoring
   For patients on corticosteroids, as a minimum this should include regular measurements of or documentation of:
   - Blood pressure
   - Weight
   - Blood glucose/HbA1c
   - Height (children)
   - Renal function
   - Evidence that gastric and bone prophylaxis is considered
   - Symptoms suggestive of important side effects, e.g. peptic ulceration, visual decline

   Other investigations are dependent on the choice of adjuvant drug but should include documentation of baseline investigations relevant to the drug in question and evidence of appropriate follow-up monitoring.

4. Adherence to guidelines for prophylaxis and management of steroid-induced osteoporosis.[82]

5. Use of objective disease-scoring methodologies to assess clinical outcomes, e.g. the pemphigus disease area index, the autoimmune bullous skin disorders intensity index or the oral disease severity score.[31-35]

The usual audit recommendation of 20 cases per department is to reduce variation in the results due to a single patient, and allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months.

29.0 SUMMARY

(See full manuscript for details of evidence)

Table 4 summarizes the treatment options for PV, highlighting certain practical and economic considerations. For an overview of PV management to serve as a brief summary of options for reference in the clinical setting see Table 1 (in section 11.0).

SUPPORTING INFORMATION

Additional supporting information including administration of rituximab and the search strategy may be found in the online version of this article.

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Footnote:

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Conflicts of interest:

None declared

Strength of Recommendation (Level of evidence)	Drug	Indication(s)	Advantages	Disadvantages	Principal side effects
B (1+)	Oral corticosteroids	The cornerstone of therapy; effective; optimum dosing schedule not known	Effective; rapid onset; oral administration; inexpensive.	Side effect profile	Diabetes; osteoporosis; adrenal suppression; peptic ulceration; weight gain; increased susceptibility to infection; mood changes; proximal myopathy; Cushing's syndrome; cataracts
B (1+)	Azathioprine	Commonly used in combination with oral corticosteroids for steroid sparing effect; monotherapy may be possible for mild disease	Oral administration; inexpensive.	Slow onset; side effect profile	Myelosuppression and nausea (related to thiopurine methyltransferase activity); hepatotoxicity and hypersensitivity reactions (unrelated to thiopurine methyltransferase activity); increased susceptibility to infection
B (1+)	Mycophenolate mofetil	An alternative to azathioprine and cyclophosphamide	Generally well tolerated and possibly less toxic compared to other immunosuppressive agents	Slow onset	Gastrointestinal disturbances (mycophenolic acid may be used as an alternative); lymphopaenia; anaemia; neutropaenia; trombocytopaenia; increased risk of infections
B (1+)	Rituximab	Patients intolerant of or refractory to conventional CS together with adjuvant immunosuppression	Effective; long lasting effect	Cost; infection risk; infusion reactions*	Risk of infection; risk of reactivation of hepatitis B; risk of precipitation of progressive multifocal leukoencephalopathy due to the JC virus; Hypogammaglobulinaemia (rare); late onset neutropenia; development of neutralising antibodies; Infusion reactions are generally mild; anaphylaxis is rare

B (2+)	Pulsed cyclophosphamide and dexamethasone or methylprednisolone	Consider for severe or recalcitrant PV; repeated courses; may not be practical	Possibly less steroid side effects than conventional CS therapy	Intravenous administration; labour-intensive; risk of bladder malignancy and infertility	Alopecia, infections; infertility; haemorrhagic cystitis; acne; hiccup
B (2++)	Intravenous immunoglobulin (IVIG)	Possible adjuvant maintenance agent for recalcitrant PV failed on other regimens; could be considered in severe cases to induce remission whilst slower-acting drugs take effect	Rapid action reported in some cases; no increased risk of opportunistic infection	Intravenous administration; very expensive; labour-intensive; theoretical risk of blood-borne virus infections	During infusion, chills, tachycardia, hypertension, muscle pains, pyrexia, nausea and headache are common, self-limited and respond to slowing the infusion; anaphylaxis is rare (increased risk in IgA deficiency)
~~B (2++) (1+)~~	~~Rituximab~~	~~Patients intolerant of or refractory to conventional CS together with adjuvant immunosuppression~~	~~Effective; long lasting effect~~	~~Cost; infection risk; infusion reactions*~~	~~Risk of infection; risk of reactivation of hepatitis B; risk of precipitation of progressive multifocal leukoencephalopathy due to the JC virus;~~ ~~Hypogammaglobulinaemia (rare); late onset neutropenia; development of neutralising antibodies;~~ ~~Infusion reactions are generally mild; anaphylaxis is rare~~
D (3)	Extracorporeal photophoresis	May be considered in recalcitrant disease where conventional treatment has failed	Can be performed via peripheral venous access	Specialist equipment; trained staff; labour-intensive; expensive; limited availability; limited data; ultraviolet protective sunglasses on the day of treatment; venous access can be a problem	Symptoms of hypovolaemia during procedure

~~D (3)~~	~~Gold~~	~~More commonly used as an adjuvant, enabling steroid dose reduction; an alternative to more established adjuvant drugs~~	~~Inexpensive~~	~~Intramuscular administration; slow onset; not commonly used~~	~~Rashes; nephrotic syndrome; myelosuppression; hypersensitivity syndromes~~
D (3)	Immunoadsorption	Should be reserved for the treatment of patients resistant to or intolerant of other approaches and should be used in combination with treatment directed at suppressing new antibody formation	Rational therapy aimed at rapidly decreasing pathogenic antibody levels; generally well tolerated	Expensive, inconvenient; rebound antibody production	Hypotension, anaphylaxis, sepsis
D (3)	Methotrexate	Could be used as an adjuvant drug if others are poorly tolerated, contraindicated or ineffective.	Oral administration; inexpensive; dermatologists very familiar with it	Slow onset	Myelosuppression; hepatotoxicity; pneumonitis
D (3)	Oral Cyclophosphamide	Could be considered as an alternative to azathioprine and mycophenolate mofetil if secondary infertility is not a concern	Inexpensive; oral administration	Potential risk of haemorrhagic cystitis and carcinoma of bladder	Neutropaenia; alopecia; gastrointestinal disturbances; raised transaminases; thrombocytopaenia; secondary infertility; nausea
D (3)	Plasma Exchange and Plasmapheresis	Not recommended as routine; may be considered for difficult cases if combined with steroids and immunosuppressants	Direct and immediate removal of IgG and therefore removal of PV antibodies	Central venous access; specialist equipment; trained staff; limited availability; labour-intensive; expensive; rebound production of PV antibodies after PE	Septicaemia; fluid and electrolyte imbalance

D (3) Historical treatment	Gold	More commonly used as an adjuvant, enabling steroid dose reduction; an alternative to more established adjuvant drugs	Inexpensive	Intramuscular administration; slow onset; not commonly used	Rashes; nephrotic syndrome; myelosuppression; hypersensitivity syndromes
D(GPP) (4)	Pulsed intravenous. corticosteroids	Consider for remission induction in severe or recalcitrant disease, particularly if unresponsive to high oral doses	Rapid onset; inexpensive	Intravenous administration	Mood changes; flushing.
Not recommended (-1)	Ciclosporin			Side effects; expensive	Hypertension; renal impairment; Gastrointestinal disturbances; hypertrichosis; hypertrophic gingivitis
Insufficient evidence (3)	Chlorambucil	Although may be used in practice further study needed before recommendation	Oral administration; inexpensive	Minimal data	Myelosuppression
Insufficient evidence (-1)	Dapsone	Although may be used in practice further study needed before recommendation	Inexpensive	Minimal data	Haemolysis; methaemoglobinaemia; hypersensitivity reactions
Insufficient evidence (-~~1~~2)	Sulfasalazine or Pentoxifylline	Although may be used in practice further study needed before recommendation	Oral administration Inexpensive	Frequent dosing (2 tablets twice daily)	Gastric pain, nausea and headache

Insufficient evidence (3)	Tetracyclines and nicotinamide	Tetracycline/ nicotinamide could be considered as an adjuvant in milder PV	Inexpensive	Lots of tablets	Flushing and headaches due to vasodilation with nicotinamide; gastrointestinal upset (tetracyclines); hyperpigmentation, particularly at sites of blistering (minocycline); discolouration of teeth (avoid tetracyclines in children and pregnant/lactating females)

Table 4: Summary of treatment options for the management of pemphigus vulgaris (PV)
*See supporting information

APPENDIX 1

LEVELS OF EVIDENCE

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal*
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

*Studies with a level of evidence '-' should not be used as a basis for making a recommendation

STRENGTH OF RECOMMENDATION

Class	Evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT: randomized controlled trial; NICE: National Institute for Health and Clinical Excellence

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